AD_____

November 5, 2013

To
Anthony M. Pacifico, Ph.D
Portfolio Manager, Medical Imaging Technologies
IPA, Battelle Memorial Institute
Telemedicine and Advanced Technology Research Center
1054 Patchel Street
Fort Detrick, Maryland 21702

RE: USAMRAA award W81XWH-09-2-0174– update of timelines and budget

Phase six of the award focuses on neurocognitive studies and imaging. This study expands on previous work and looks to specifically compare proton therapy with advanced conventional therapy such as Intensity Modulated Radiation Therapy (IMRT) for patients with low grade glioma of the brain and for patients with base of skull (BOS) meningioma.

Current status- Over the past year, Michelle Alonso-Basanta, MD, has continued as Principle Investigator of this protocol. We have completed the development of a clinical protocol that covers the entire project, and the protocol was revised for scientific and operational clarity in 9/2011. Early in the second year, eligibility requirements were updated to include patients with diseases of different histologies, and these changes were approved by both the Penn IRB and the DOD Review Board. The minimum radiation dose was also decreased to 45 Gy. These changes will facilitate our meeting target accrual on time. A total of 21 patients have been enrolled: 8 patients in the skull base cohort 1 [2 female photon and 6 (2 male; 4 female) protons], 4 female and 1 male patient in the low grade glioma/meningioma cohort 2 and 9 (6 male, 3 female) control patients. We continue to achieve continuous enrollment with 4 of the above 22 patients enrolled during the most recent quarter (July, August, September 2013). Below is a breakdown of accrual by year and cohort.

Year	**2009**		**2010**		**2011**		**2012**		**2013**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Cohort 1	0	0	0	0	0	0	1 (27)	3 (31-32)	1 (21)	3 (46-57)
Cohort 2	0	0	0	0	0	2 (37-62)	1 (37)	1 (47)	0	1 (28)
Control	0	0	0	0	0	1 (25)	3 (31-45)	0	2 (35-57)	3 (27-59)

M=male
F=Female
(xx)=age or age range

All patients have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, all patients have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. The majority of patients have completed baseline and at least two additional time-points in regards to both neurocognitive testing and MRI. Preliminary results are presented as part of this report.

2011 Q4 – enrollment initiated
2012 Q1 until 2014 Q2- continue enrollment and studies with relaxation of enrollment criteria
2014 Q2- continue enrollment and studies of low grade glioma. Complete BOS study

2014 Q3- until 2015 Q2- continue enrollment and studies
2015 Q3- complete study

An updated version of the budget is attached. Please do not hesitate to contact me directly with any questions or concerns.

Sincerely yours,

Christine Hill-Kayser MD
Project Manager
Assistant Professor of Radiation Oncology
University of Pennsylvania
Tl: 215-662-7771
Fax: 215-349-5445
Email: hill@uphs.upenn.edu

Zelig Tochner MD
Medical Director, Roberts Proton Therapy Center
University of Pennsylvania Medical Center
Tl: 215-662-7147
Fax: 215- 615-5449
Email:tochner@uphs.upenn.edu

Carolyn Kendall
Associate Director, Pre-Award
Office of Research Services
University of Pennsylvania
P221 Franklin Building
3451 Walnut Street
Philadelphia, PA 19104-6205
Phone:(215) 898-9323
Fax: (215) 898-9708

CC: Anthony M. Pacifico, Ph.D
Portfolio Manager, Medical Imaging Technologies
IPA, Battelle Memorial Institute
Telemedicine and Advanced Technology Research Center
1054 Patchel Street
Fort Detrick, Maryland 21702

Award Number: W81XWH-09-2-0174

TITLE: Neurocognitive Effects of Radiotherapy

PRINCIPAL INVESTIGATOR: Michelle Alonso-Basanta, MD

CONTRACTING ORGANIZATION: Trustees of the University of Pennsylvania,
Pamela Caudill
3451 Walnut Street
Room FP221 Franklin Building
Philadelphia PA 19104-6205

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Carol Armstrong PhD, Manoj Kumar PhD, , Harish Poptani PhD, Michelle Alonso-Basanta MD, Zelig Tochner MD, Ron Wolf MD PhD, Tim Zhu PhD, Lilie Lin, MD, Alexander Lin, MD; Robert Lustig, MD; Peter Gabriel MD, Christine Hill-Kayser, MD

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14. ABSTRACT

This report describes continued work on the award "Neurocognitive Effects of Radiotherapy", which examines the neurocognitive and imaging impact of proton therapy for patients will low grade glioma and base of skull meningioma. A total of 21 patients have been enrolled: 8 patients in the skull base cohort 1 [2 female photon and 6 (2 male; 4 female) protons], 4 female and 1 male patient in the low grade glioma/meningioma cohort 2 and 9 (6 male, 3 female) control patients. We continue to achieve continuous enrollment with 4 of the above 21 patients enrolled during the most recent quarter (July, August, September 2013). All patients have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, all patients have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. The majority of patients have completed baseline and at least two additional time-points in regards to both neurocognitive testing and MRI.

Although data are preliminary, neurocognitive results for 15 subjects (9 proton, 6 control) indicate no indication of deterioration in procedural learning or complex attention from pre-proton baseline to 1.5 months after completing radiation based on the Serial Response Test and Audiovisual Attention Shift task, respectively. The Timing Function (TF) test indicates that patients may be less accurate in time perception than controls; however, it also demonstrates a trend of recovery in this skill from pre-proton baseline to 1.5 months after radiation. All three of these tests are experimental and require validation in this particular setting. Based on these preliminary data, all three appear reliable, with the TF test appearing most sensitive for change over time in patients, while providing stable results in controls. Imaging analysis has been carried out independently from neurocognitive analysis. Preliminary imaging data demonstrate that hippocampal imaging changes appear to correlate well with tumor location (preservation of the contralateral hippocampus after radiation). Review of FA data suggest that midline BOS tumor treatment does not result in hippocampal changes on FA, but that treatment of brain parenchymal tumors may cause differences on FA based on laterality of the tumor and the radiation. Similar observations have been made with regard to blood perfusion based on rCBV values. Correlation of imaging and neurocognitive data will be undertaken in the upcoming year.

A component (10%) of this award supports the Walter Reed Army Medical Center scientists. Dr. Michelle Alonso-Basanta is Principle Investigator for this. Susan Prendergast is the Clinical Research Coordinator managing the associated IRB-approved protocol. Dr. Christine Hill-Kayser is the Project Manager for this section of the award. Further budgetary details are outlined in the attached document.

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Introduction

The overall goal of this multi-year research project in collaboration with the Walter Reed Army Medical Center is to develop the necessary technology to make the proton facility in Philadelphia the most advanced proton radiotherapy center. Award # W81XWH-09-2-0174 comprises phase 6 of this endeavor and consists of the following clinical study:

Neurocognitive protocol

Preliminary data suggest that regions of the normal brain exposed to radiation doses that has otherwise been regarded as safe and not limited by current radiation treatment planning may contribute to the risk of late neurocognitive injury. Radiation dose-dependent subclinical vascular effects have been reported in irradiated normal brain tissue and have been hypothesized to be a potential mechanism of action. Direct neuronal injury is another potential mechanism of injury. **Purpose:** 1) To estimate the degree of cognitive loss following radiation therapy. 2) To determine if clinical variables (including medications, age, mood disturbance, fatigue, chemotherapy, neurological and cerebrovascular comorbidities) correlate with memory decline as measured by neurocognitive testing in a prospective longitudinal study using a similar neurocognitive test battery. 3) To describe radiotherapy dose-related changes in vascular perfusion, in spectroscopic parameters of neuronal injury, and in changes in the degree and directionality of tissue water diffusivity (diffusion tensor imaging). 4) To correlate the MRI findings in regions of interest (ROIs) with neurocognitive changes, focusing initially on changes in memory. **Methods:** Eligible subjects will include patients with tumors (benign or malignant) of the skull base or patients with low grade glioma or meningioma who require radiotherapy. 10 subjects receiving photon treatment plans and 20 subjects receiving proton treatment plans with tumors (benign or malignant) involving the base of skull and a total of 40 patients with low grade glioma or meningioma will be prospectively enrolled. Baseline perfusion, spectroscopic, and diffusion MRI imaging of the brain utilizing established techniques will be used to identify and characterize the regions of interest (ROI) anatomically adjacent to the regions of intended high dose irradiation. The MRI data for the ROIs will be registered with the radiotherapy treatment planning CT in order to create a single volume of data where each voxel corresponds to a vector containing the multi-parametric information. Subsequent repeat MRI imaging will be approximately at 1.5, 6, 12, and 24 months following completion of the radiotherapy for patients. Both cohorts will repeat standard neurocognitive evaluation at approximately 1.5, 6, 12 and 24 months following completion of radiotherapy. A normal, control (non-diseased) group will have 70 subjects. This normal group will not have radiotherapy. This group will only have neurocognitive evaluation at enrollment (baseline) and approximately 3 months from baseline. **Analysis:** Neurocognitive domains will be evaluated at the designated time points. These will include: verbal and visual memory; immediate attention, working memory, and processing speed; executive functions and affect and depression. The primary analysis will be to evaluate within-patient changes from baseline to one year.

Body

The Hospital of the University of Pennsylvania, in collaboration with Walter Reed Army Medical Center, is building the most advanced cancer treatment facility in the world. This will be a fully-integrated facility utilizing state-of-the-art imaging and conformal treatment techniques including proton radiotherapy. Research projects with the intent of full implementation of end products are required to reach the full potential of proton therapy. In the original statement of work first of five planned projects were identified, to be implemented on a yearly basis to provide the most advanced cancer treatment facility in the world. Each of these projects will help advance proton therapy worldwide and result in measurable benefits. The projects identified were:

(1) Multi-leaf collimator (MLC) for use on proton therapy gantries

(2) Cone Beam CT on the Gantry for localization of target volumes

(3) Proton Radiography to determine dose and stopping power of various tissues

(4) Positron Emission Tomography (PET) imaging on the gantry to evaluate dose deposition within tissues irradiated

(5) Scanning proton beam using adaptive radiotherapy techniques based on implementation of MLC, Cone Beam CT, PET imaging.

A major aim of the entire project is to provide the most advanced radiation therapy to military personnel and their immediate families; the facility opened for patient treatment in January, 2010.

Much of this work has been initiated in earlier phases of this award. Phase 1 concentrated on designing and building a Multi-leaf collimator for use in proton therapy. Phase 2 focused on studying the optimal way to use scanned proton beams. The purpose of Phase 3 was to include the ideas of adaptive radiotherapy techniques and to define the role of imaging in proton therapy including the introduction of on-gantry cone beam CT (CBCT). The integration of these techniques, redefined as image guided proton therapy (IGPT) and adaptive proton therapy (APT) was a major aim of the phase 3 proposal. Phase 4 "Proton Therapy Dose Characterization and Verification" investigates the use of PET to verify dose distributions from proton beams as well as characterizing the radiobiological effect. Phase 5 "Development of Technology for Image-Guided Proton Therapy" is designed to bring to proton radiotherapy some techniques, such as cone-beam CT and Calypso localization, which are available in conventional radiotherapy.

The current work (phase 6) investigates the effect of radiotherapy using serial MRI imaging and a series of neuropsychological measurements on two groups of patients; (1) those with base-of-skull , and (2) those with low-grade gliomas or meningiomas.

Progress

1. The first year's effort was dedicated to constructing an approved protocol to be used to

study patients via MRI and neurocognitive testing. After revision for scientific and operational clarity, the protocol was approved by the Institutional Review Boards of both Penn and the DOD. Additionally, immobilization equipment that enables us to deliver base-of-skull treatments optimally was developed.

2. Having completed these tasks, we initiated patient recruitment in September, 2011.
3. Early in the second year, eligibility requirements were updated to include patients with diseases of different histologies, and these changes were approved by both the Penn IRB and the DOD Review Board. The minimum radiation dose was also decreased to 45 Gy. These changes will facilitate our meeting target accrual on time. Over the second year, 10 further patients were enrolled. A total of 21 patients have been enrolled: 8 patients in the skull base cohort 1 [2 female photon and 6 (2 male; 4 female) protons], 4 female and 1 male patient in the low grade glioma/meningioma cohort 2 and 9 (6 male, 3 female) control patients.
4. The majority of patients have completed baseline and 2 additional timepoints of neurocognitive testing and MRI, although the data are not mature enough to allow definitive analysis. Included is preliminary data on the cohorts as of October 2013.
5. Michelle Alonso-Basanta continues to serve as Principle Investigator.

Appendix I. Summary of Preliminary Data

2013 Annual Progress Report 0174:
Detection of Vascular and Neuronal Changes and their Correlation to Neurocognitive Changes following Proton and Photon Radiotherapy in Patients Receiving Skull Base and Brain Radiation.

This is an annual summary report of the UPCC #08310, on which patient enrollment began in October 2011. Early in the second year, eligibility requirements were updated to include patients with diseases of different histologies as well as decreasing the minimum radiation dose to 45 Gy. This facilitated continued enrollment and plan for target accrual. We have attempted to minimize visits outside of the protocol requirements to assist most of the "out of town" patients to consider enrollment as we discovered that most patients did not want to make additional trips. Patients currently enrolled have commented that this has been helpful.
A total of 21 patients have been enrolled: 8 patients in the skull base cohort 1 [2 female photon and 6 (2 male; 4 female) protons], 4 female and 1 male patient in the low grade glioma/meningioma cohort 2 and 9 (6 male, 3 female) control patients. Included is accrual by year below.

Year	2009		2010		2011		2012		2013	
	M	F	M	F	M	F	M	F	M	F
Cohort 1	0	0	0	0	0	0	1 (27)	3 (31-32)	1 (21)	3 (46-57)
Cohort 2	0	0	0	0	0	2 (37-62)	1 (37)	1 (47)	0	1 (28)
Control	0	0	0	0	0	1 (25)	3 (31-45)	0	2 (35-57)	3 (27-59)

M=male
F=Female
(xx)=age or age range

All patients have completed a 4-5 hour neurocognitive testing assessment at baseline by Dr. Carol Armstrong. In addition, all patients have completed a 1 hour standard MRI as well as additional testing including diffuse tensor imaging (DTI), perfusion and diffusion. The majority of patients have completed baseline and at least two additional time-points in regards to both neurocognitive testing and MRI. Dr. Harish Poptani and Manoj Kumar have been overseeing every MRI obtained at each timepoint. Evaluation of MRI changes is currently being done independently of neurocognitive testing and preliminary results are presented below. Joint discussions continue as we are now meeting every 3 months to discuss evaluations as patients complete the study in its entirety.

Neurocognitive Testing: Preliminary Results (10/2013)
Serial Response Test (SRT): The SRT is a classic test of procedural learning, a type of implicit cognition that has been associated with the cerebellum and the basal ganglia. The subject is presented with a screen with 4 blank circles aligned in a diamond array. Each time the circle in filled in, the subject must push the button corresponding to that

position. In the first block of 56 trials, the stimuli appear in a random order in regards to their positions. In blocks 2, 3, and 4, each of 56 trials and unknown to the subject, the stimuli appear in a repeating order of an 8-trial sequence, repeated 7 times. In block 5, the stimuli again appear in a random order. After a period of learning, the subjects' responses will optimize by the 4th block. When the stimuli become random again on block 5, response time slows again. We analyze Block5-Block4; a positive value is one indicator of the learning effect, such that the greater the value, the greater the learning effect.

Data are presented showing the comparison of patients (n=9) and controls (n=6) in their response time differences between blocks 5 (T5) and 4 (T4). There was no significant change in patients change in reaction time (Figure 1, t test, p=0.28) between Time 1 (baseline testing) and Time 2 (1.5 months after completion of radiation). However, their accuracy improved between the two time points (Figure 2, t test, p=0.02). These results reveal no deterioration in patient cognition on procedural learning from pre-proton baseline to 1.5 months after full dose.

Figure 1 – Reaction time

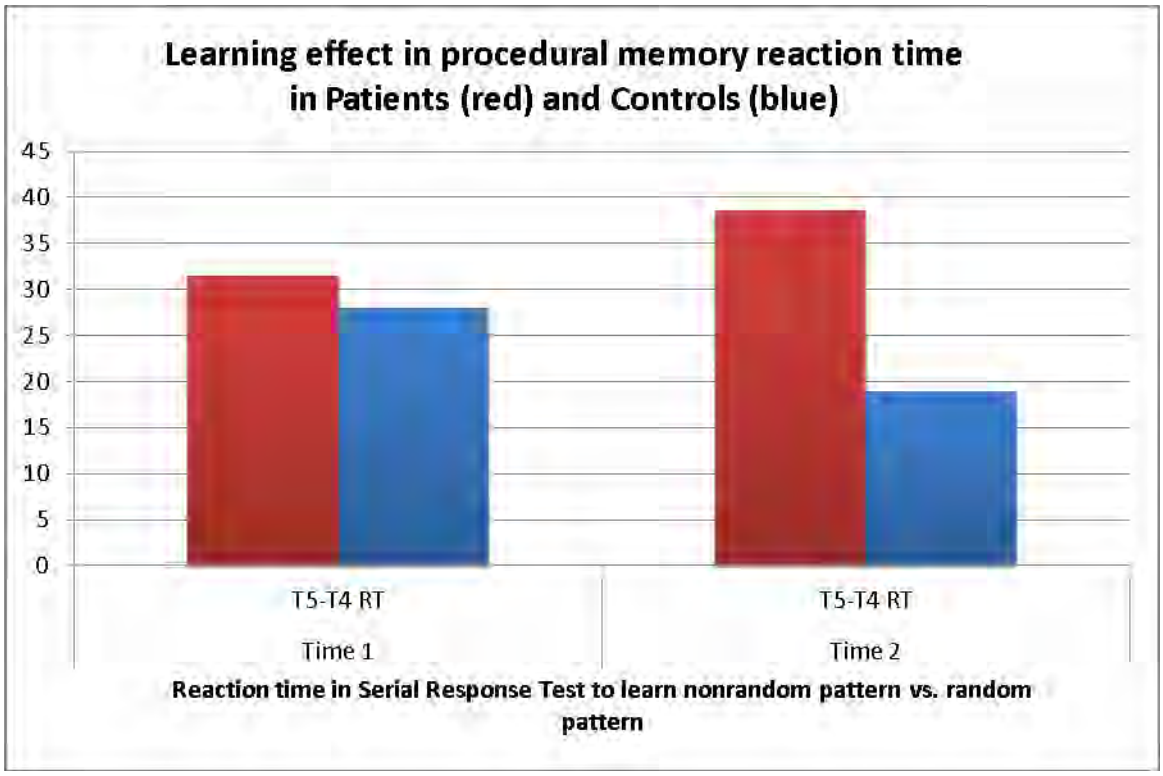
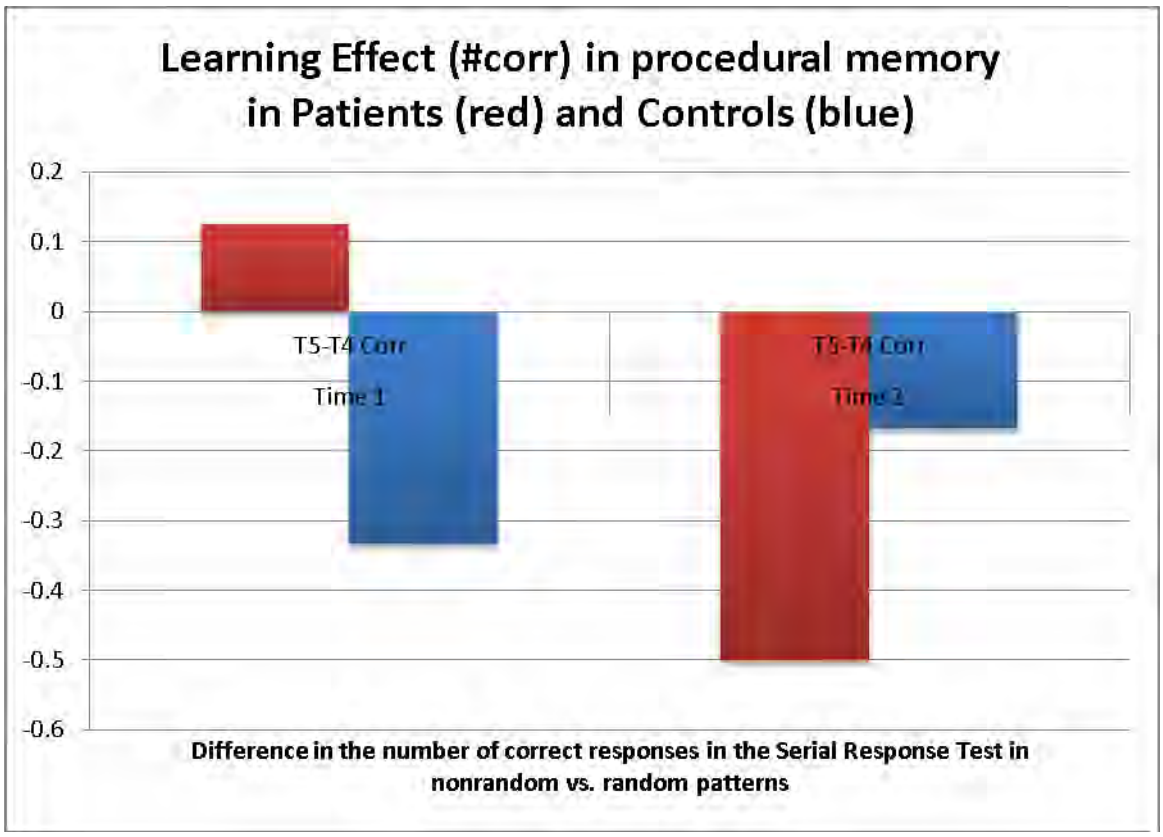
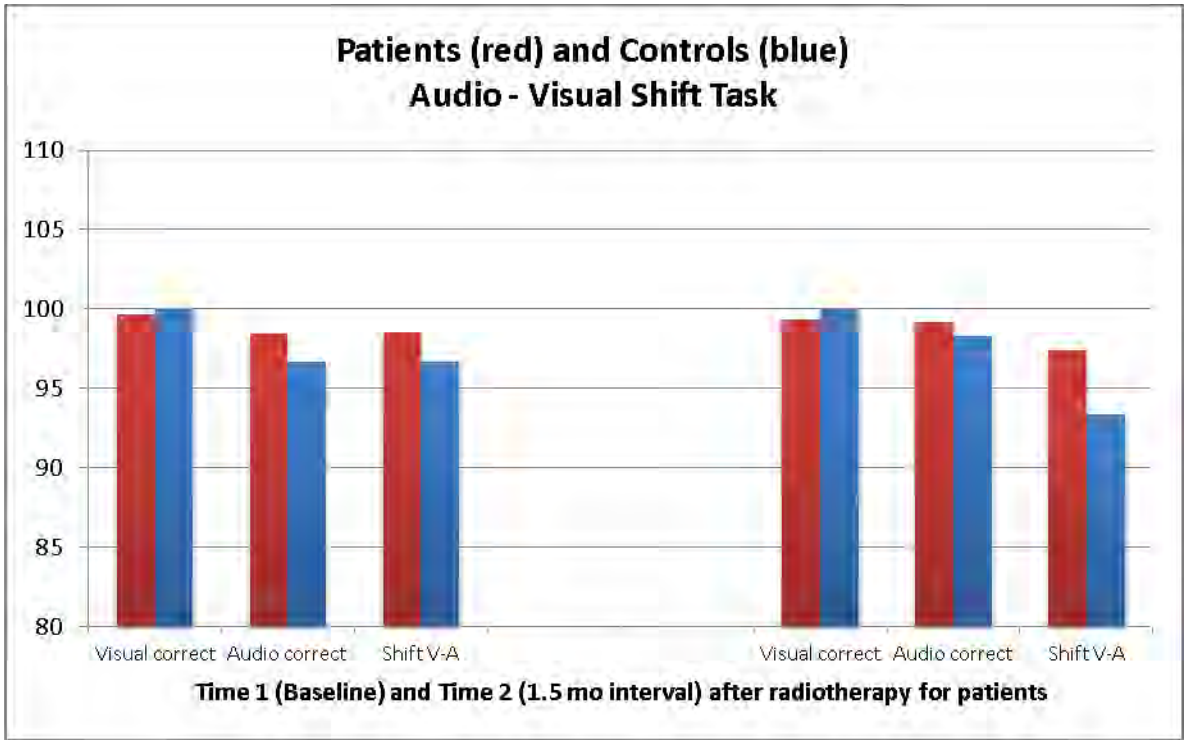


Figure 2 - Accuracy



Audio Visual Attention Shift Task (AV Shift): The AV Shift task tests the accuracy of focusing on a visual target only, an auditory target only, or in shifting between the targets within the same trial. This paradigm has been sensitive to individuals with autism, who typically have reduced cerebellar volumes. In the first test, the subject must press a key when a red box appears (intermixed with green boxes and high and low tones). In the second test, the subject must press when a low tone is heard (intermixed with red boxes, green boxes, and high tones). In the third test, the subject responds to the red boxes when signaled to "look", and to the low tones when signaled to "hear". Interstimulus intervals are of mixed lengths, and analyses will examine if patients have greater difficulty when inter target stimuli are of longer than shorter intervals.
Data are presented showing the performances of patients (n=9) and controls (n=6) of their accuracy in responding to the targets for visual only, audio only, or shifting visual and auditory. No changes were found in patients' ability to detect visual targets (t test, p=0.15), auditory targets (t test, p=0.32), or to switch between visual and auditory targets (t test, p=0.15). This data describes no decline in complex attention from pre-proton baseline to 1.5 months after completion of full dose.

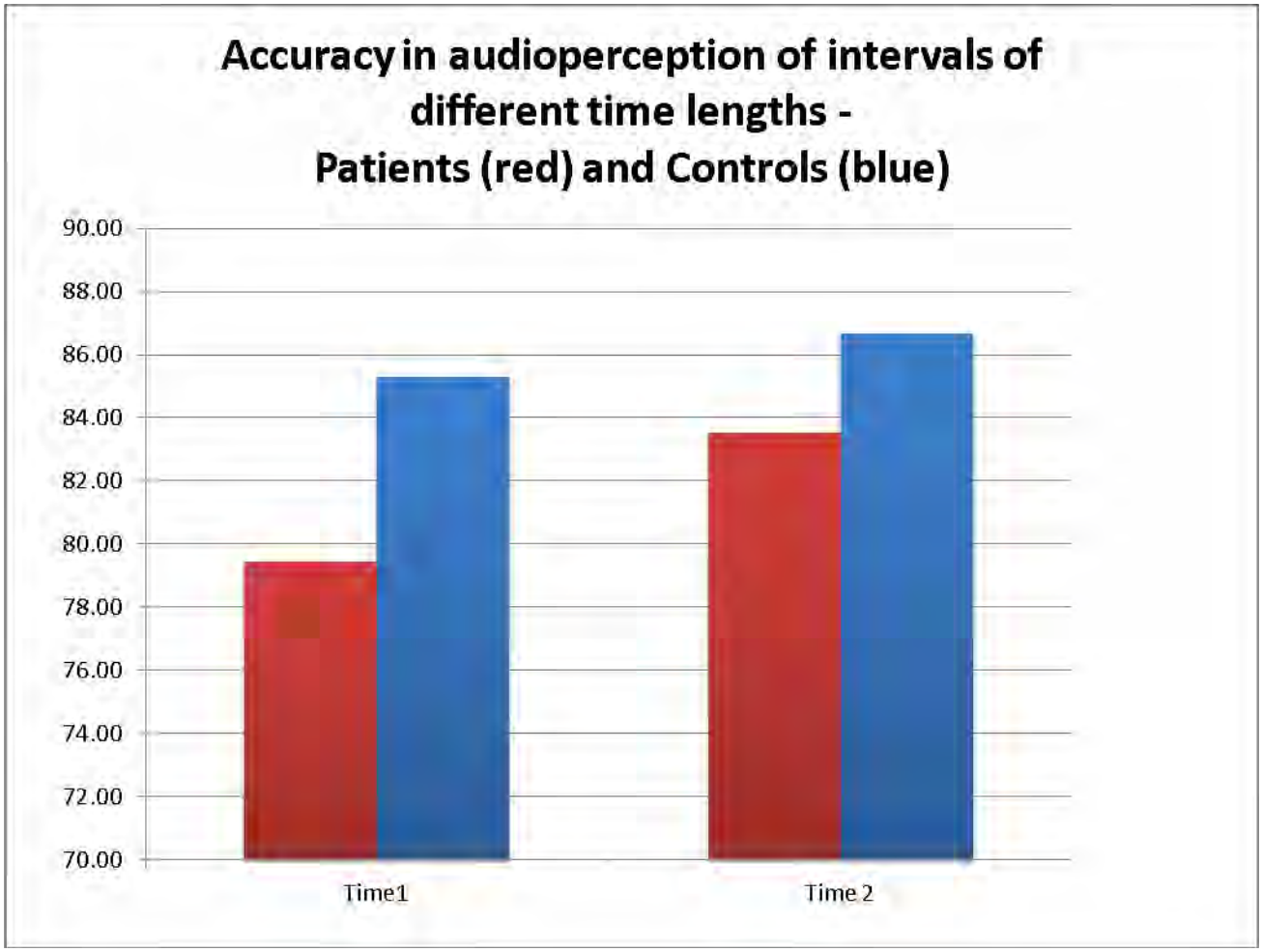
Figure 3 – Reaction Time



Timing Functions (TF): The TF has two parts: the first measures a motor control function in which the subject must imitate an evenly timed pacing of tones by pressing the key simultaneously to the tones, and then continuing the timing when the tones end. This data is not presented, and this timing function is not considered to be critically controlled by the cerebellum. The second task analyzes the subjects' perception of timing by discriminating various time intervals between two tones as compared to a standard time interval between tones. The intervals between the test tones range from barely discernable to clearly discernable, and between longer than the standard tones and shorter than the standard. The perception of timing has been most strongly associated with cerebellar timing functions.

Data are presented for both patients (n=9) and controls (n=6) cases without missing values, on the average accuracy of perception of both the tone pairs that are longer and shorter than the standard. The data show that patients are less accurate than controls, but also demonstrate a trend of recovery in time perception after baseline (t test, p=0.05) in patients from pre-proton baseline to 1.5 months after full dose. Data also demonstrate the reliability of control performance over the two time periods.

Figure 4 - Accuracy



Summary:

The experimental tests of cerebellar cognition are the most innovative aspect of the cognitive studies, and as such, the tests need to be validated for the purpose of testing for radiation effects. They were given to normal controls over two time periods to test their intra-subject reliability. We need to see reliability in the control data, before trying to interpret the patterns seen in patients. We present data on 3 of the 4 tests.

TF appears the best candidate for having the needed reliability for comparison with patients receiving radiation; using t tests to compare whether results in controls changed between time 1 and time 2, results were found to be stable in controls ($p=0.31$). It also appears to have the needed sensitivity because the patients are significantly more impaired than controls at baseline ($p<0.03$). However, all three cerebellar tests seemed reasonably reliable (Serial Response, $p=0.30$; AV Shift, $p=0.18$).

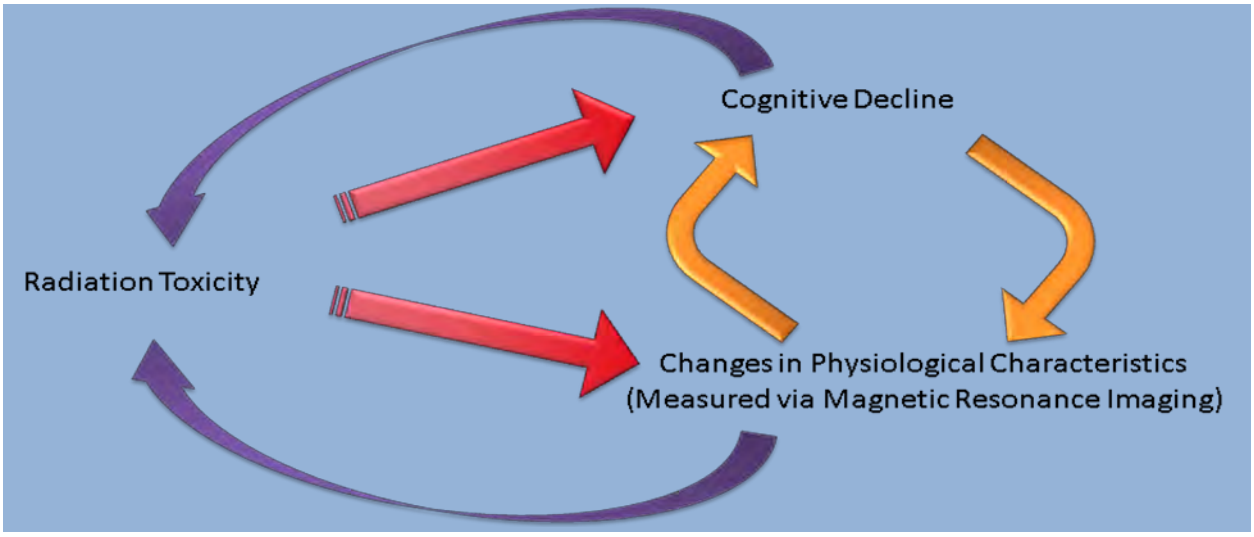
This sample of patients demonstrated either no change, or improvement in cognition (perception of timing) on the three experimental, cerebellar specific tests.

MRI Evaluation: Preliminary Results (10/2013)

MRI evaluation also began at this time and was independent of neurocognitive and clinical data so as to not bias any changes noted from baseline.

Briefly, our hypothesis is that changes in physiology in the hippocampus, cerebellum and possibly other anatomic locations in the brain and base of skull, as measured by magnetic resonance imaging (MRI) will correlate with change in cognitive decline and to radiation-induced damage (Figure 5).

Figure 5



There are various parameters that can be measured with MRI and will briefly be described. As the signal is given off by relaxation of the excited protons in the body, we can obtain the diffusion tensor imaging (DTI) which includes parameters such as the Apparent Diffusion Coefficient (ADC) or the Fractional Anisotropy (FA). ADC is the mean diffusion outwards from a relative point and describes the cellular density of that voxel. The FA gives us unidirectional diffusion and allows us to measure the directional component of the diffusion. Alternatively, we can also obtain the Dynamic Susceptibility Contrast (DSC) which allows us to measure the Relative Cerebral Blood Volume (rCBV). This describes the blood volume in a region of interest and is an indicator of vascularization (or lack there-of) relative to white matter.

In our preliminary analysis, we reviewed the changes noted in the hippocampus bilaterally. Figure 6 shows the ADC for 12 patients at various time-points. Of note, there are limited data on many of these patients as they may have had only 1 or 2 time-points done in addition to baseline. Time 0 is baseline testing (pre-radiation) with each timepoint thereafter describing the time-points of the study (e.g. time 1=1.5 mo from completion of radiation, time 2=6 mo from completion, etc). Figure 6a shows the changes from baseline of the right hippocampus, Figure 6b shows the changes from baseline of the left hippocampus.

Figure 6a

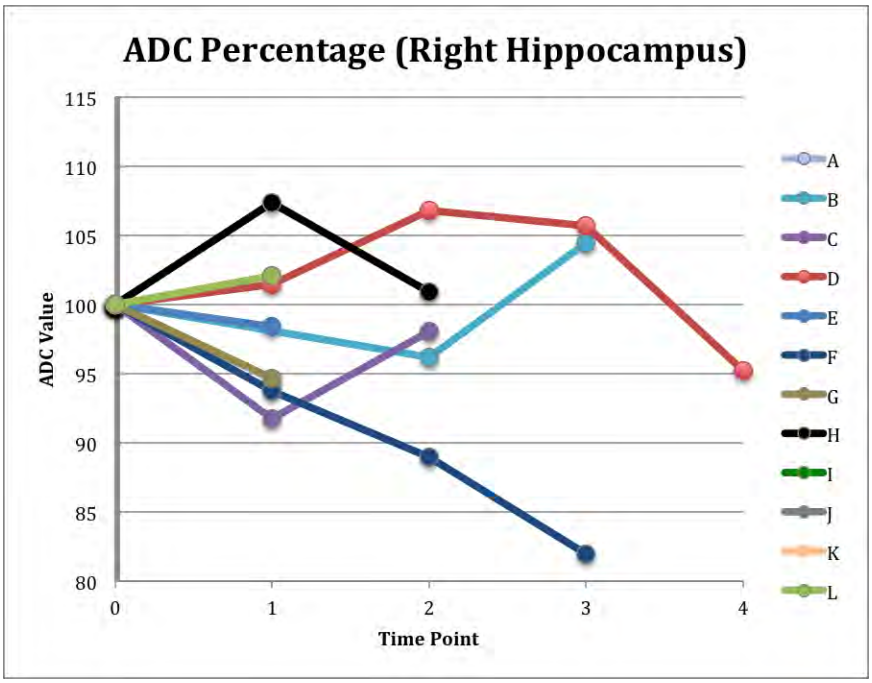
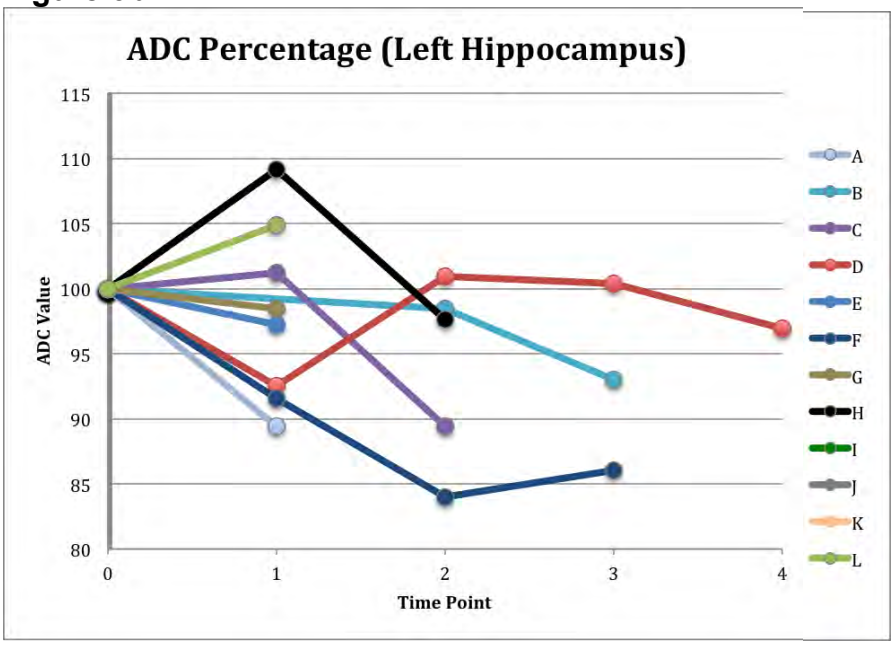
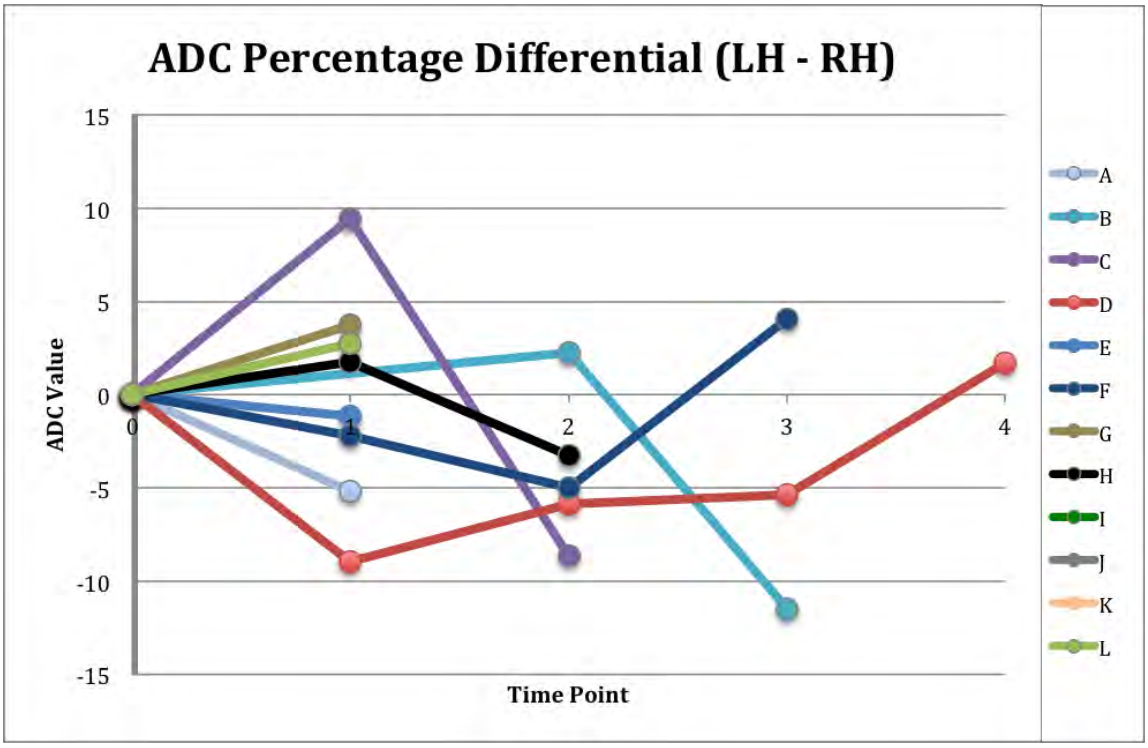


Figure 6b



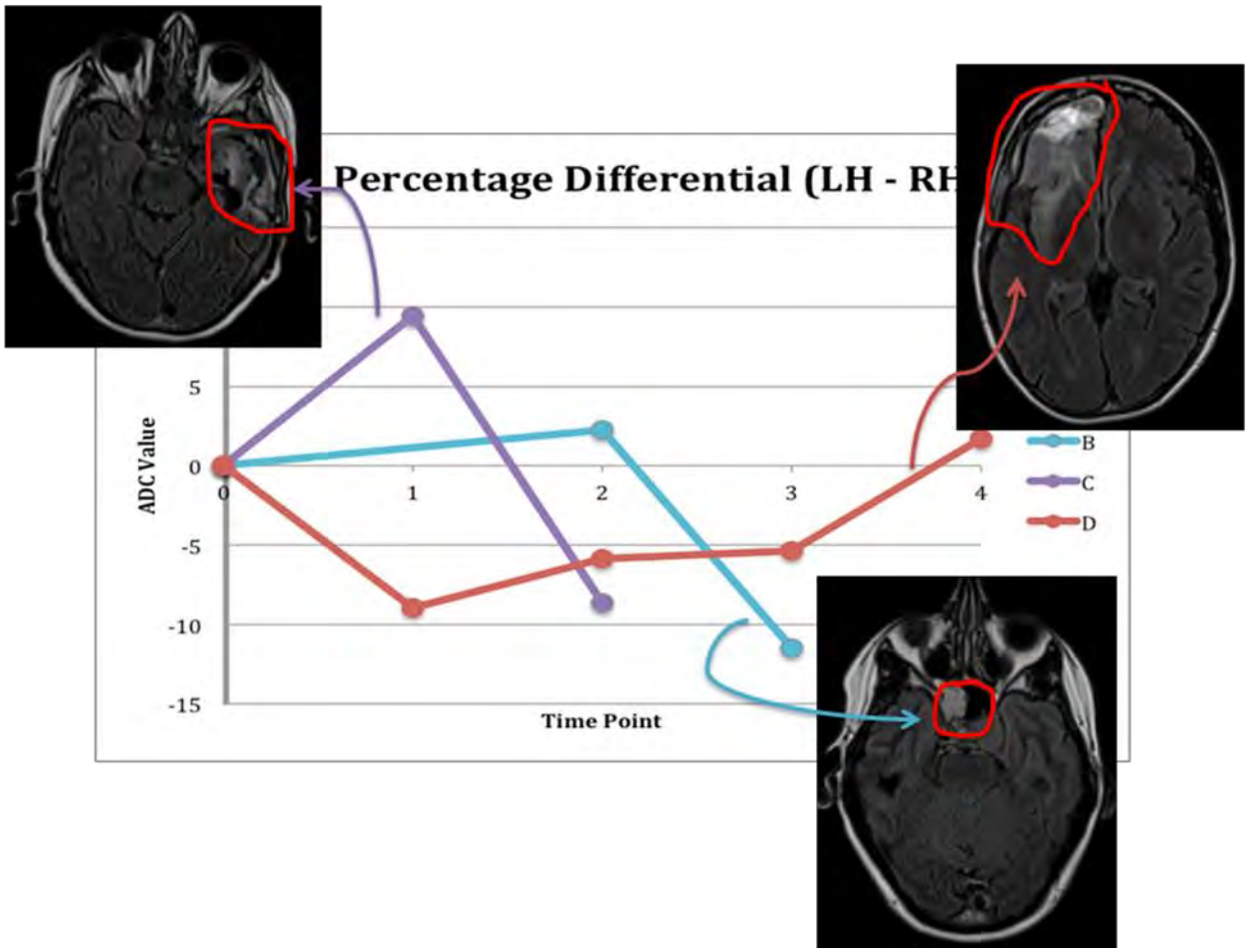
As can be seen, there are a number of patients with changes noted in ADC with patient E having a change and recovery in the left hippocampus but persistent change in the right hippocampus. When we review the differential difference (Figure 7), patients B through E have significant changes noted.

Figure 7



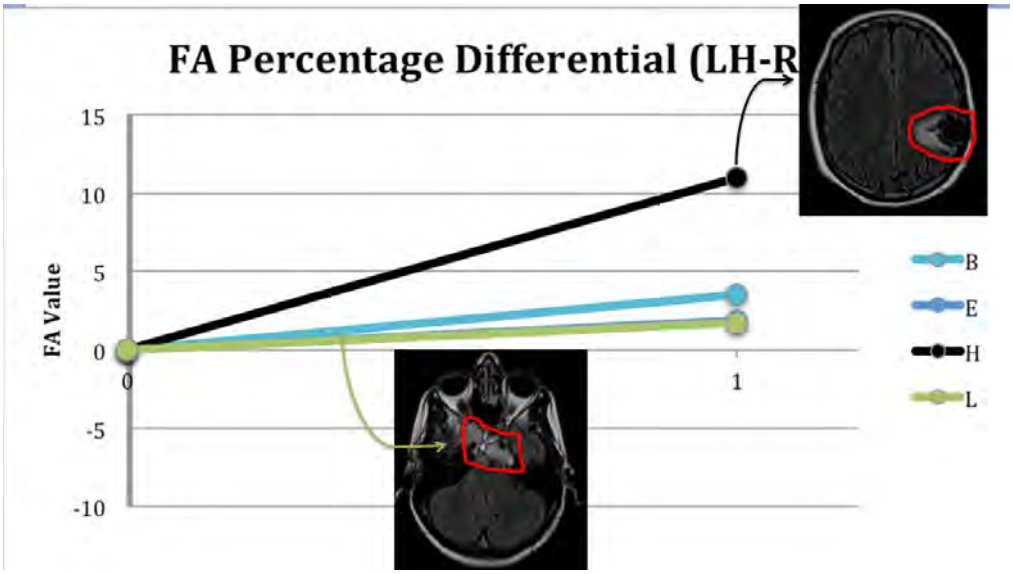
We therefore further reviewed the findings of three patients and correlated location of tumor to changes noted on ADC (Figure 8). On preliminary review, the changes noted correlate well with location of tumor as left sided tumors show preservation of the right hippocampus and right sided tumors show preservation of function on the left hippocampus. We will need to next correlate these changes with any neurocognitive changes in the patient and this analysis is currently ongoing.

Figure 8



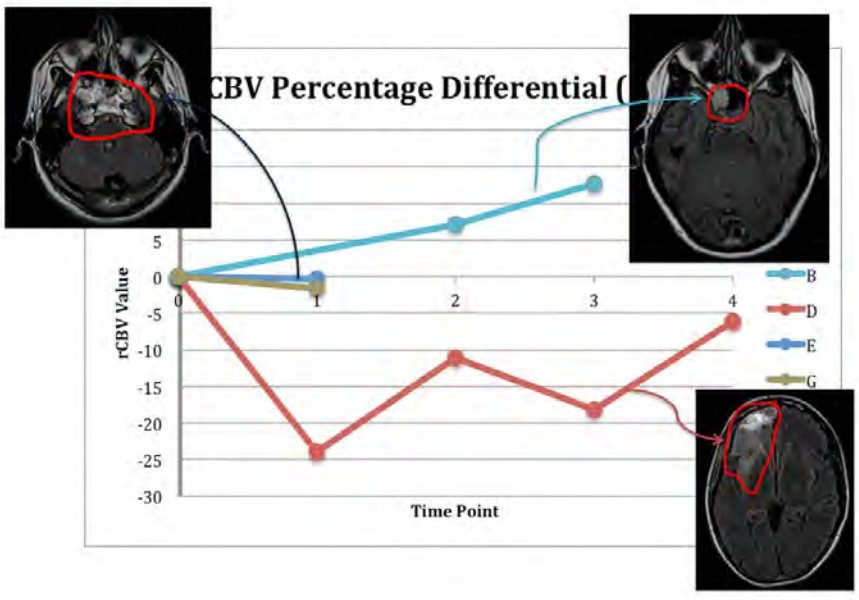
We then reviewed the FA value differential for these patients (Figure 9). The data are quite preliminary but suggests, as hypothesized, that skull base tumors – usually midline tumors – will have no difference in FA in the hippocampus however tumors in the brain parenchyma, with laterality, will have a change or direction (FA) noted between the left and right hippocampus.

Figure 9



We have also reviewed the rCBV value differential for these patients (Figure 10). This is very preliminary data but again notes a change in blood perfusion between the left and right hippocampus based on location. It suggests that midline bilateral tumors have no difference in rCBV in the bilateral hippocampus however tumors in the brain parenchyma or BOS tumors with laterality, will have a change rCBV noted between the left and right hippocampus.

Figure 10



Summary

With regard to our cognitive data at this time, we have preliminarily reported on the patient group as a whole and have not begun analysis on each individual cohort. This will be done as each cohort acquires additional data from testing throughout the next few years. In addition, we have only compared the groups at one time point. It will be interesting to see how this changes over time for each patient cohort.

The MRI data were analyzed independently of the neurocognitive and clinical data so as to not bias the evaluation. We are only just beginning to review the changes seen on MRI with clinical parameters and correlating those to individual neurocognitive results. We would anticipate having more data and information in this regard for the annual report next year.

Appendix II. Protocol

CLINICAL RESEARCH PROTOCOL

CLINICAL RESEARCH

Detection of Vascular and Neuronal Changes and their Correlation to Neurocognitive Changes Following Proton and Photon Radiotherapy in Patients Receiving Skull Base and Brain Radiation

SPONSOR: This study is being funded by a grant from the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

Protocol Number:	IRB #811792; UPCC #08310
Principle Investigator:	Michelle Alonso-Basanta
Co-Investigator(s):	Harish Poptani Manoj Kumar Ronald Wolf Tim Zhu Carol Armstrong Lilie Lin Alexander Lin Robert Lustig Zelig Tochner Christine Hill-Kayser Peter Gabriel
Biostatistician	Rosemarie Mick

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List of Abbreviations

RT	radiation therapy
cGy	centigray
IMRT	intensity modulated radiotherapy
IMPT	intensity modulated proton therapy
MRI	magnetic resonance imaging
fMRI	functional magnetic resonance imaging
ROI	region of interest
fROI	functional region of interest
NAA	N-acetyl aspartate
Cho	choline
Cr	creatine
rCBV	relative cerebral blood volume
rCBF	relative cerebral blood flow
FA	functional anisotropy
ADC	apparent diffusivity coefficient
MD	mean diffusivity
MNI	Montreal Neurological Institute
PI	Principal Investigator
AE	Adverse Event
SAE	Serious Adverse Event
GI	Gastrointestinal
IRB	Institutional Review Board
USAMRMC	US Army Medical Research and Material Command
ORP	Office of Research Protection
HRPO	Human Research Protection Office

Study Summary

Title	Detection of Vascular and Neuronal Changes Following Proton and/or Photon Radiotherapy in Patients Receiving Skull Base and/or Brain Radiation
Short Title	Skull base and Brain neurocognitive MRI study
Protocol Number	UPCC # 08310; IRB # 811792
Phase	Not applicable
Methodology	Prospective, 2 cohorts, non-randomized
Study Duration	3 years active enrollment
Study Center(s)	Single-center
Objectives	Primary Objective: To estimate the degree of memory loss, if any, following radiotherapy to the base of skull or brain as measured by standard neurocognitive battery testing. To describe radiotherapy dose-related changes in vascular perfusion, in spectroscopic parameters of neuronal injury and changes in the degree and directionality of tissue water diffusivity (diffusion tensor imaging) as a measure of white matter axonal injury. To relate these imaging characteristics to the degree of memory loss.
Number of Subjects	30 cohort 1; 40 cohort 2; 70 normal group
Diagnosis and Main Inclusion Criteria	For cohort 1: Eligible study subjects will include subjects with a histological diagnosis of a tumor (benign or malignant) of the base of skull necessitating irradiation to a minimum of 45 Gy, ECOG PS 0-1 with no evidence of metastatic disease and an estimated life expectancy of at least 1 year and who is able to provide informed consent. Subjects will undergo standard CT simulation and radiotherapy treatment planning. For cohort 2: Eligible study subjects will include patients with a histological diagnosis of low grade glioma or meningioma requiring radiotherapy. ECOG PS 0-1 with no evidence of metastatic disease and an estimated life expectancy of at least 1 year and who is able to provide informed consent. Subjects will undergo standard CT simulation and radiotherapy treatment planning.
Statistical Methodology	Graphical methods and descriptive statistics will be generated to understand data quality and characterize distributions of the outcomes. Pearson's correlation will be employed to assess correlation between imaging and neurocognitive measures taken at the same time points. Within-patient changes between pairs of time points will be tested by paired t test. Within-patient trends over time will be analyzed with linear mixed effects models. Trends over time will be compared between groups using linear mixed effects models, in which a time by group interaction term is included.

Abstract: Preliminary data suggests that regions of the normal brain exposed to radiation doses that has otherwise been regarded as safe and not limited by current radiation treatment planning may contribute to the risk of late neurocognitive injury. Radiation dose-dependent subclinical vascular effects have been reported in irradiated normal brain tissue and have been hypothesized to be a potential mechanism of action. Direct neuronal injury is another potential mechanism of injury. **Purpose:** 1) To estimate the degree of cognitive loss following radiation therapy. 2) To demonstrate evidence of radiation induced subclinical vascular and neuronal injury in adjacent brain regions receiving exit doses of radiation. **Methods:** Eligible subjects will include patients with tumors (benign or malignant) of the skull base or patients with low grade glioma or meningioma who require radiotherapy. 10 subjects receiving photon treatment plans and 20 subjects receiving proton treatment plans with tumors (benign or malignant) involving the base of skull and a total of 40 patients with low grade glioma or meningioma will be prospectively enrolled. Baseline perfusion, spectroscopic, and diffusion MRI imaging of the brain utilizing established techniques will be used to identify and characterize the regions of interest (ROI) anatomically adjacent to the regions of intended high dose irradiation. The MRI data for the ROIs will be registered with the radiotherapy treatment planning CT in order to create a single volume of data where each voxel corresponds to a vector containing the multi-parametric information. Subsequent repeat MRI imaging will be approximately at 1.5, 6, 12, and 24 months following completion of the radiotherapy for patients. Both cohorts will repeat standard neurocognitive evaluation at approximately 1.5, 6, 12 and 24 months following completion of radiotherapy. A normal, control (non-diseased) group will have 70 subjects. This normal group will not have radiotherapy. This group will only have neurocognitive evaluation at enrollment (baseline) and approximately 3 months from baseline. **Analysis:** Neurocognitive domains will be evaluated at the designated time points. These will include: verbal and visual memory; immediate attention, working memory, and processing speed; executive functions and affect and depression. The primary analysis will be to evaluate within-patient changes from baseline to one year.

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Background

Standard **photon** radiation when administered for skull base and brain will result in exit radiation to adjacent normal brain tissue. This is due to the physical nature of the photon radiation depositing its energy along its entire physical path-length. Modern computer-based radiation treatment planning seeks to limit the risk of brain injury by conforming the radiation such that the total cumulative doses of radiation that is allowed to exit into the adjacent brain is sufficiently low to limit the risk of brain injury. However, the dose limit that is typically used is for the risk of developing **brain necrosis**. In general, radiation doses less than 60 Gy to the brain have been considered to be safe for this risk. Recent investigations have demonstrated that neurocognitive injury without the presence of brain necrosis, or **subclinical injury**, is a risk with both brain [1,2] and skull base radiation [3,4] and that this may occur at lower radiation doses typically regarded as safe. The mechanism(s) for this type of injury is largely unknown and has not been well studied.

Proton radiotherapy is unique in that the dose deposited along its physical path-length can be modulated with the entire radiation dose deposited at a defined depth significantly reducing the dose of radiation to adjacent normal tissue distal to this peak of radiation, referred to as the **Bragg peak**. As such, it becomes relevant to characterize the nature and the extent of any subclinical brain injury arising from skull base and brain radiation. This research protocol seeks to apply advanced MRI imaging techniques to temporally characterize these changes in the brain and to correlate the observed changes to the radiation dose and to determine if these also correlate with clinical manifestations of neurocognitive injury. This protocol will prospectively enroll two groups of patients: 1) subjects with **skull base** tumor**s** (benign or malignant) treated with current state of the art conformal photon radiation techniques using **intensity modulated radiation therapy** (IMRT) followed by the enrollment of subjects treated with protons as this is gradually introduced into clinical practice at the Roberts Proton Therapy Center at the University of Pennsylvania and 2) patients with low grade gliomas or meningiomas who receive proton radiotherapy.

Radiation Induced Brain Injury:

Parameters that exacerbate or moderate radiation injury are: (1) host factors of age, white matter risk, and genetic risk; (2) the temporal phase of the effects: acute, early-delayed, and late-delayed, (3) concurrent clinical factors, such as hypertension and diabetes, (4) the radio therapeutic technique (e.g., whole brain versus proton therapy), and (5) cellular radiosensitivity. There is accumulating evidence that several mechanisms account for brain injury caused by irradiation. Radiation alters the permeability of the blood brain barrier (bbb) via the vascular endothelial cells. Glial cells are also moderately sensitive resulting in disruption of neural myelination and of transmission of neuronal signals. Increases in microglia in the hippocampal microenvironment are part of an immunologic inflammatory process that is also thought to cause injury[5]. Decrease in neuronal progenitor cells has also been observed in the hippocampus, which is a structure critical for memory. Injury is continuous, dynamic, and interactive with other tissues, especially hypoxia/ischemia, and inflammation [6].

Clinical radiation injury is considered to have three distinct phases. This study focuses on the early-delayed and late-delayed phases. The early-delayed phase is sub acute, occurs weeks to months after treatment is completed, and may be followed by recovery of functions. Late-Delayed effects are not reversible, occur years after radiotherapy is completed, are often devastating, and can involve diffuse effects on brain structure and functions. Longitudinal structural brain imaging has shown that the most common type of injury is comprised of diffuse and sometimes progressive changes in the white matter. While glial injury, demyelination, and necrosis may be confined to the white matter, both grey and white matter is affected by vascular changes. It is very difficult to predict the severity of radiation injury that can be expected, even when the total dose and dose burden is known because of little known clinical factors that also influence the severity and timing of injury. Vascular injury and

glial atrophy may occur at a later time point than demyelination. Therefore, there are many types of possible radiation injury, but white matter is most vulnerable [7].

Cognitive effects of photon radiation injury:

It is thought that the early-delayed phase of radiotherapy results in temporary damage to the semantic associative memory network supported by the neocortex [8]. In a brain tumor group-controlled, prospective, longitudinal study, only two measures of semantic memory demonstrated a significant change over time in the RT-treated group, although a comprehensive neuropsychological battery of repeatable measures, heavily weighted with memory and attention measures, was given to all patients. The slope of change described a decline six weeks after completion of radiotherapy (early-delayed period) followed by a rebound. The two radiotherapy-related measures were the post-encoding retrieval from long-term memory of semantic material (meaningful words and meaningful and nameable pictures). Both these measures require widespread semantic networks for retrieval, and suggest that a mechanism of temporary damage to the neocortex as well as to the hippocampus might be responsible for the early-delayed injury from radiotherapy. There are no reports of the effects of proton radiotherapy on brain structure or on cognitive functions.

The late-delayed cognitive effects are more variable; symptoms are irreversible and probably progressive [9]. The onset of changes have been retrospectively described several months to many years post treatment [10,11]. There are few prospective studies of the late-delayed time points in patients with nonmalignant disease. Studies of patients with low-grade brain tumors, whose disease causes less damage at baseline than malignant tumors, report much less significant damaging effects on cognition 2-4 years after treatment [7,12]. While retrospective reports and individual case studies demonstrate the severity that late-delayed damage from RT can cause, there is little information on the actual frequency of such severe damage. MRIs showed mildly increasing white matter hyper intensities and white matter atrophy over the first three years post treatment with unclear progression. The few cognitive studies that exist indicate radiation-specific injury that is progressive. Injury and progression appear to be specific to individuals who carry risk factors. In general, cognitive risks, as discriminated from progressive injury due to neoplastic malignancy, appear selective to memory [7,12,13].

Some patients will receive radiotherapy to the cerebellum as part of their standard care. There are no extant studies of the neurocognitive effects from irradiation of the cerebellum.

Neuroimaging measurement of damage from photon radiotherapy:

A vascular mechanism for radiation induced subclinical brain injury was suggested by Price and colleagues who demonstrated a significant dose-related reduction in the relative blood volume and flow in adjacent normal brain regions in 4 subjects receiving conformal standard fractionated irradiation for low-grade gliomas at 3 months [14]. MR dynamic contrast susceptibility perfusion imaging of predetermined anatomic regions of interest (ROI) in the white matter was correlated with the summarized radiotherapy doses to these ROIs. No significant changes in blood flow (rCBF) or volume (rCBV) was seen in regions receiving less than 32 Gy with significant differences seen greater than 4 months and receiving more than 43 Gy. The rCBF and rCBV were normalized to the baseline studies. At 42 days, imaging demonstrated that the rCBF and rCBV tended to be higher with higher radiation doses (> 43 Gy) and at 132 days, consistently lower in white matter regions receiving higher radiation doses. No neurocognitive testing was performed.

Direct subclinical evidence of neuronal injury which may or may not be independent of vascular injury has also been demonstrated with radiation to the brain as characterized by the use of MRI proton spectroscopy [15-17]. The long-term clinical significance of these changes is unclear at this time. Sundgren and colleagues reported the results of a prospective study of 11 subjects with low grade or benign tumors imaged serially with a 2D multivoxel MR spectroscopic technique out to 6 months [15]. All patients were treated 1.8 Gy daily, Monday to Friday, for 28-33 fractions, resulting in 50.4-59.4 Gy to the tumor. Signs of occult neuronal injury were seen as early as 3 weeks during a course of radiotherapy as demonstrated by significant decreases in the NAA/Cr and Cho/Cr ratios. These metabolites remained significantly decreased out to 6 months. The metabolite NAA (N-acetyl-aspartate) is believed to represent a marker of neuronal density and function and its progressive reduction over time (especially at 6 months) suggests that the process of neuronal damage continued long after the completion of RT. Choline is a marker of cell membrane biosynthesis and its metabolic turnover and is felt to reflect glial cell proliferation. There was no correlation with the dose delivered when analyzed at 6 months except for a relationship between the

decreases in the Cho/Cr ratio up to 1 month from completion of the radiotherapy and larger volumes of normal brain receiving higher doses (>40 Gy).

Collectively, these limited studies are provocative in suggesting that modern advanced imaging techniques that assess the function of the brain offer the potential to better understand the mechanism of subclinical radiation-induced changes to the brain. Subclinical neuronal damage can be detected but it is unclear if these are separate of any vascular injury. The risk of vascular injury may be dose-related and possibly more likely to be a dominant mechanism of injury at higher radiation doses. The inter-relationship between the risk of neuronal injury, vascular changes and radiation dose has not been well studied and is important to characterize to determine to what extent the application of proton radiotherapy treatment planning may help to reduce this risk.

Low Grade Gliomas:

There are approximately 8,000 new low grade gliomas (LGG) diagnosed each year in the United States **Central Brain Tumor Registry of the United States** (CBTRUS)[18]. These include astrocytomas, oligodendrogliomas and mixed tumors. There is no consensus as to the appropriate treatment for these tumors. Treatments include surgery, biopsy or resection, radiation, and chemotherapy, or a combination of these treatments. In the era of enhanced imaging technologies, some physicians have advocated for early intervention with surgery, radiotherapy and/or chemotherapy; however, the optimal timing and sequencing of these therapies remains unclear.

There are two main issues in the management of LGGs with respect to radiotherapy: timing (at diagnosis vs. at progression) and appropriate radiation dose. There are 3 randomized trials on the use of radiation for the treatment of LGG. Shaw et al[19] reported on the results of Radiation Therapy Oncology Group (RTOG) 8602, which was a randomized study of high dose (64.8 Gy/36 fractions) vs. low dose (50.4 Gy/28 fractions) radiotherapy immediately following resection in patients with LGG. This study included 203 patients treated from1986 to 1994. Survival at 2 and 5 years was non-significantly better in the low dose group (72% v 64%, respectively). The European Organization for Research and Treatment of Cancer (EORTC) trial 22844, Karim et al [20]l, reported on 379 adults with LGG randomized to either 45Gy or 59.4Gy in 1.8Gy fractions. They found no difference in overall survival for patients receiving low dose vs. high dose radiotherapy, 58% vs. 59%, respectively or in progression free survival 47% v 50%, respectively. The minimum follow up was 50 months with a median of 74 months. Early versus delayed post operative radiation was explored in (EORTC) 22845[21]. Following surgery, patients were randomized to either immediate radiation therapy to 54Gy or delayed radiation of the same dose delivered at the time of progression. Three hundred and fourteen patients were randomized. Progression free survival was 5.3 years in the early radiation group versus 3.4 years in the delayed group. Median survival was 7.4 years in the early group and 7.2 years in the delayed group. In the delayed group 65% of the patients received radiation at the time of progression. It was also noted that at one year seizures were better controlled in the early radiation group.

Prognostic factors for patients with LGG were analyzed by Pignatti et al[22]. They reviewed patients with LGG treated in EORTC studies 22844 and 22845. Relevant factors include age greater or less than 40, tumor size, greater or less than 6cm, tumor crossing the midline, histological subtype, and pre-surgery neurologic deficit to be determinants of outcome. Chang et al[23] reported on a group of 281 adult patients with LGG treated at the University of California at San Francisco. They developed a preoperative prognostic scoring system using age greater then 50, Karnofsky Performance Status (KPS) 80 or less, tumor location in an eloquent area, or a tumor over 4cm. Based on their system 3 separate groups could be identified.

The role of chemotherapy for patients with LGG is still uncertain. RTOG 9802 randomized high risk LGG patients following surgery to either radiation to 54Gy or to radiation followed by 6 cycles of Procarbazine, Lomustine, and Vincristine (PCV). The early reports show an improvement in progression free survival for induction chemotherapy but no improvement in overall survival.[24] There is no clear consensus at this time exactly what role chemotherapy should play in the treatment of newly diagnosed LGG.

Kiebert et al[25] reported on quality of life (QOL) post radiation in EORTC study 22844. This was a secondary non-mandatory end point. Only 180 of 379 randomized patients completed at least one QOL form. This study only reported data on the initial, 3, 6, and 12 month time points as there were too few forms filled out at later time points. In general, patients receiving the high dose radiation reported lower functioning levels and higher symptom burdens. The groups were significantly different for fatigue and insomnia immediately post therapy with approximately 40% reporting severe fatigue in the lower dose arm and 55% in the higher dose arm. A difference in leisure time and emotional functioning at 7-12 months also favored the lower dose arm. Klein et al[13] attempted to

evaluate the effect of radiation and other treatment factors on long term cognitive outcomes in LGG patients. The study compared 195 LGG patients, 104 of whom had received radiation, to 100 patients with low grade hematological malignancies. LGG patients had lower ability in all cognitive areas compared to low grade hematological patients and the disparity was even worse when the LGG patients were compared to healthy controls. Cognitive disability in the memory domain was found only in radiation patients treated with fractions greater than 2Gy. The use of antiepileptic drugs was strongly associated with impairment in attentional and executive function. However, Surma-aho et al[26] reported on patients with LGG who had either surgery only or surgery followed by radiation. The group who received radiation demonstrated poorer cognitive function and lower KPSs. There is no prospective quality of life data or prospective neurocognitive studies on patients with LGG treated with proton beam radiation. There are also no prospective studies on the incidence and severity of fatigue in this group of patients.

The Kibert[25] study showed a dose response in 2 domains of QOL. Therefore, the ability of proton beam radiation to deliver an extremely conformal dose to the tumor while allowing very significant sparing of normal tissue should allow for similar local control rates as photon beams but with improved neurocognitive outcome and better QOL. The significant reduction of the integral dose of radiation to the brain may also lessen the incidence and degree of fatigue reported in patients with brain tumors treated by radiation therapy.

Potential Impact of Proton Radiotherapy Treatment Planning:

Of the two published studies that have examined the impact of skull base radiation on neurocognition, one series studied the impact of proton irradiation for chordomas and low-grade chondrosarcoma and were prospectively evaluated with baseline and follow-up neurocognitive evaluations [4]. The median prescribed tumor dose was 68.4 CGE. The other represented a retrospective report of the impact of traditional photon treatment planning for carcinomas of the paranasal sinus with post-treatment neurocognitive evaluation delivering more than 60 Gy [3]. In the group treated with proton irradiation at the skull base, no significant changes in various neurocognitive domains were seen with the last evaluation at approximately 7 months from the end of treatment [4]. In contrast, in the group receiving 60-70 Gy for paranasal sinus carcinomas, patient performance was significantly below that expected with tests of memory function [3]. There is a suggestion that in part, the difference in neurocognition may have been related to the mean dose delivered to the hippocampus with the group receiving protons having a maximum dose ranging between 34 to 44 Gy compared to >60 Gy in the group with neurocognitive deficits.

Summary:

Subclinical neuronal and vascular changes in adjacent normal brain tissue receiving exit radiation can be identified with the application of serial advanced imaging techniques especially with MRI techniques that offer the ability for multi-parametric evaluation. The ability to draw more generalized conclusions from these studies is limited for several reasons including the small study populations, the lack of neurocognitive evaluation and the potential confounding effects of the tumor on the surrounding normal brain tissue under study.

As such, this project will evaluate a patient population with skull base tumors that will reduce the influence of tumor on the normal brain tissue whose prognosis will facilitate long-term follow-up evaluation. Additionally, we will evaluate a group of patients with low grade gliomas and meningiomas to understand what if any long-term cognitive decline can be mitigated with proton beam radiotherapy.

The interpretation of deficits found in neurocognitive testing as it relates to the radiation dose is fundamentally a clinically relevant research relationship which is limited by the anatomic localization of regions of the brain involved in specific neurocognitive tasks. As a secondary objective, we will apply MRI techniques to both characterize the underlying nature of the brain injury but also to help improve the localization of regions that may be involved in specific neurocognitive tasks.

We anticipate that as protons are gradually introduced into clinical practice and as the more conformal **intensity modulated proton therapy technique (IMPT)** is technically developed, we will be able to assess if protons may reduce the subclinical injury characterized with conformal photons such as IMRT.

Our proposed study will include three cohorts: 1) patients with tumors involving the skull base who may have incidental radiation dose to adjacent normal brain, and 2) patients with low grade glioma or meningioma receiving radiotherapy. 3) In addition, there will be a normal group of patients that will undergo neurocognitive testing at two timepoints for cerebellar comparison.

Risk/Benefits

NEURO-COGNITIVE TESTING RISKS: Neuro-cognitive testing can cause fatigue in some individuals. It is possible that a subject could have anxiety regarding test performance.

MRI RISKS:

The risks of magnetic resonance imaging studies are minimal. The levels of energy used to make magnetic resonance measurements are far less than are used in a single X-ray, and many people have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic while inside the magnet. If the subject becomes uncomfortable inside the magnet, they may withdraw immediately from the study.

The greatest risk is a metallic object flying through the air toward the magnet and hitting the subject. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once the subject is in the magnet, the door to the room will be closed so that no one will accidentally walk into the magnet room.

During some of the MRI scans, subjects have occasionally reported temporary tingling or twitching sensations in their arms or legs, especially when their hands are clasped together. Because of the strong magnetic field, people with pacemakers, metal fragments in the eye, or certain metallic implants cannot participate in this study. The subject will be given a checklist before entering the MRI room, to obtain a history that the subject does not have a contraindication.

One part of the study may require injection of a contrast agent (or "dye") called gadolinium through a temporary IV in the hand or arm, and this is the same contrast agent used for routine clinical studies. The IV (intravenous) contrast agent is routinely given during clinical exams, and has been approved for that purpose for many years. The main risk is of a reaction to the IV contrast agent, and such a reaction is exceedingly rare. In light of recent reports of a possible risk of nephrogenic systemic fibrosis (NSF, also referred to as nephrogenic fibrosing dermopathy or NFD) occurring following administration of a Gadolinium-based contrast agent, subjects with known moderate to severe renal disease will be excluded from the research study. (See Attachment B for calculation method)

PREGNANCY RISKS:

Although there are no known risks of MRI to pregnant women or the fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, pregnant women are not eligible to participate in this study. If the subject is a woman of child-bearing potential, a negative pregnancy test (urine) will be required before participation in this study.

ABNORMAL FINDINGS:

These studies are part of a research study and are not intended to provide a comprehensive clinical MRI examination of the brain. In the unlikely event that a significant brain abnormality is found while processing the subject's brain images for the research study, the subject will be contacted and we will arrange for an appropriate medical referral.

The benefits associated with the research project is limited to the advancement of knowledge about the risks and the nature of subclinical radiation induced brain injury and determining if this is clinically relevant in subjects with gliomas, meningiomas and skull base tumors (benign or malignant). There is no anticipated direct benefit to the study subject. In summary, the risks associated with the imaging studies are modestly greater than minimal risk with efforts established to minimize these risks. The risks associated with neurocognitive testing are minimal. The potential benefits with knowledge derived from the diagnostic interventions include the development of ways to apply protons to minimize the risk of functional neurocognitive injury. Insights gained will likely have relevance in the development of pharmaceutical radioprotectants. As such, this offers a favorable risk-benefit assessment for this research plan.

Study Objectives

Primary Objectives

To estimate the degree of cognitive loss, if any, following radiotherapy to the base of skull or brain as measured by standard neurocognitive battery testing using a prospective, longitudinal design beginning prior to radiotherapy (approximately baseline), and then approximately 1.5, 6, 12, and 24 months post completion of radiotherapy.

2.1.1 To determine the neurocognitive change in patients with tumors (benign or malignant) involving the base of skull who receive proton beam radiotherapy, as compared to a contemporary group of patients treated with photon beam radiotherapy.

2.1.2 To determine the neurocognitive change in patients receiving proton beam radiotherapy for low grade glioma or meningioma as compared to a historical group of patients who have received photon beam radiotherapy in the University of Pennsylvania Longitudinal Study of Radiation Effects on Cognition[7,27] as measured by prospective, longitudinal neurocognitive testing.

Secondary Objectives

2.2.1 To determine if clinical variables (including medications, age, mood disturbance, fatigue, chemotherapy, neurological and cerebrovascular comorbidities) correlate with memory decline as measured by neurocognitive testing in a prospective longitudinal study using a similar neurocognitive test battery.

To describe radiotherapy dose-related changes in vascular perfusion, in spectroscopic parameters of neuronal injury, and in changes in the degree and directionality of tissue water diffusivity (diffusion tensor imaging).

To correlate the MRI findings in regions of interest (ROIs) with neurocognitive changes, focusing initially on changes in memory.

Study Design

General Design

The study design will prospectively enroll study subjects to a research MRI/neurocognitive study with 2 cohorts, consisting of subjects who have skull base tumors (benign or malignant) and subjects who have low grade gliomas or meningiomas. Subjects will have MRI imaging and neurocognitive evaluation at approximately baseline, at the approximately 1.5, 6, 12 and 24 months after the completion of the radiotherapy. The table below outlines this schedule. The baseline studies will be coordinated to avoid delays in the start of the standard oncologic treatment.

	Evaluation	Baseline	Approx 1.5 months from day of last RT tx	Approx 6 months from day of last RT tx	Approx 12 Months from day of last RT tx	Approx 24 months from day of last RT tx
Base of Skull (n=30)	Standard of Care MRI	X	X	X	X	X
	Advanced Imaging	X Research	X Research	X	X	X

				Research	Research	Research
	Neurocog testing	X Research	X Research	X Research	X Research	X Research
Low Grade Glioma or meningioma (n=40)	Standard MRI	X	X	X	X	X
	Advanced Imaging	X Research	X Research	X Research	X Research	X Research
	Neurocog testing	X Research	X Research	X Research	X Research	X Research

* Visits will occur at time points based on time of baseline visit (approximately the three months for normal controls and approximately 1.5 months post treatment end date for treatment cohorts)

Standard Treatment

For patients with skull base tumors (benign or malignant) (cohort 1), treatment will consist of daily fractionated radiotherapy utilizing an IMRT technique at the time of initial study accrual. As experience with proton therapy increases its application will be introduced to the skull base at which time subjects treated with protons as a component of their treatment will be enrolled. The total dose prescription will be dependent on the clinical indications. This will reflect whether or not surgery was performed and the pathologic features necessitating post-operative irradiation. Study subjects may or may not receive concurrent chemotherapy depending on the clinical indications.

For patients with low grade gliomas or meningiomas (cohort 2), treatment will be with protons alone.

Normal subjects will not receive radiotherapy.

Study Subject Enrollment

The study will enroll subjects to two cohorts.

	Photon	Protons
Number of Subjects Cohort 1	10	20
Number of Subjects Cohort 2:		40

The normal group will participate only in a portion of the neurocognitive testing, for a total n=70. The normal subject group will be matched in age and education with the cohort groups.

Research Imaging

MRI Protocol

Patients will have the following clinical MR imaging protocols on the Department of Radiation Oncology 1.5 Tesla MR Scanner. Imaging time will be 60-90 minutes in duration. An intravenous line will be placed to facilitate the administration of gadolinium. Standard MRI precautions will be undertaken to minimize risks typically associated with imaging in a 1.5T magnet.

Anatomic Imaging:

Standard structural imaging sequences, including axial 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE) pulse sequence before and after contrast, sagittal 3D T2-weighted, and axial Fluid Attenuated Inversion Recovery (FLAIR) pulse sequence.

Blood volume measurements:

Dynamic susceptibility contrast (DSC) PWI will be obtained during the first pass of a 12ml bolus of gadodiamide (Omniscan™)contrast agent followed a loading dose of 3ml gadodiamide (gradient echo EPI, GRAPPA with acceleration factor of 2, TR/TE 2000/45msec, slice thickness 3mm, voxel size 1.72x1.72x3mm^3, 20 slices).

Diffusion Tensor Imaging:

DTI will be acquired with a 12-direction, single shot, spin-echo echo planar sequence. Imaging parameters were as follows: 6500/99, field of view (FOV) 22 x 22 cm^2, 3mm slice thickness, 128 x 128 matrix, b values = 0 and 1000 s/mm^2 and 40 slices covering the whole brain. The acquisition time for the DTI images was about 8 minutes.

DTI Image Processing~~:~~

Three eigenvalues and eigenvectors of diffusion tensors for each pixel were calculated using multivariate fitting with "DTI-Task-Card" (Version 1.69, MGH, Boston, MA). Subsequently, ADC and FA maps were calculated according to equations (1) and (2), respectively.

ADC = ([illegible] (1)

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \qquad (2)$$

MRS:

Single slice 2D multivoxel ^{1}H MRSI will be performed using a spin echo sequence with water suppression using a TR/TE = 1700/30ms, NEX = 3, field of view =16x16 cm^2, BW=1200 Hz, matrix size = 16x16. The volume of interest (VOI) will be selected such that to include the enhancing region as well as peritumoral region of the neoplasm and contralateral normal parenchyma avoiding the scalp, skull base or sinuses. Eight outer volume saturation slabs (30mm thick) will be placed outside the VOI to suppress lipid signals from the scalp. Both water suppressed and unsuppressed ^{1}H MRSI spectra will be acquired and the unsuppressed water signal will be used for computing metabolite concentrations.

MRS Data Analysis

All ^{1}H MRS data will be analyzed using a user-independent spectral fit program [Linear Combination (LC) Model]. The region between 0.2 and 4.0 ppm of the spectrum will be analyzed and the following metabolites will be evaluated: N-acetyl aspartate (NAA) 2.02ppm; Cr, 3.02 ppm; Cho, 3.22 ppm; glutamate+glutamine (Glx), 2.24-2.34ppm; myo-inositol (mI), 3.56 ppm. The NAA/Cr, Cho/Cr and NAA/Cho ratios will be computed.

Neuropsychological Measurements

University of Pennsylvania Longitudinal Study Cognitive Battery:

Attention:

1. Audio-Visual Attention Shifting T. – speed and accuracy in shifting attention from auditory to visual to inputs[29];

Associative and Long-Term Memory:

3. Rey Auditory Verbal Learning T.,
4. Biber Figure Learning T. [30],
5. Picture Recognition T. [31];
6. Hopkins Verbal Learning Test

Procedural Learning:

7. Serial Response Task – reaction time to learn an implicit sequence [32];
8. Semantic Fluency Test (Animals);

Executive and Conceptual Processes:

9. Balls in a Bottle Test – an inferential reasoning task[33],
10. Timing Functions T. – perception of time intervals [34];
11. Trails B
12. Phonemic Fluency Test

Visuomotor Scanning Speed:

13. Trails A

Mood, fatigue:

14. Fatigue Severity Scale[35],
15. Beck Depression Inventory,
16. Beck Anxiety Inventory.

Primary Study Endpoints

A priori hypotheses about memory will be tested in the mixed model as expected slopes of linear change over time.

Secondary Study Endpoints

Correlations with regional imaging measurements/quantitations will first be tested with domain composite scores. Individual hypotheses about association of cognition with radiation sensitive brain structures, such as the hippocampus and cerebellum, will exploit individual neurocognitive functions. For example, we expect a relationship, such as the relationship of associative memory to hippocampus quantitations, and serial response learning to cerebellar quantitations.

Blood volume measurements will be summarized by determining the rCBV (relative cerebral blood volume) and rCBF (relative cerebral blood flow).

Spectroscopy measurements will be summarized by the metabolic ratios NAA/Cr, Cho/Cr and NAA/Cho.

Diffusion tensor imaging will be summarized by the fractional anisotropy (FA). Diffusivity will be summarized by the apparent diffusivity coefficient (ADC), mean diffusivity (MD), parallel and perpendicular averaged water diffusivity.

Primary Safety Endpoints

There are no primary safety endpoints as this is not a therapeutic intervention study.

Subject Selection and Withdrawal

Inclusion Criteria for Cohort 1 (Patients with tumors (benign or malignant) involving the base of skull)

Study subjects capable of providing informed consent.

Study subjects with an ECOG performance status of 0-1 or KPS of 60-100.

Study subjects aged 18 or greater.

Study subjects with a histological diagnosis of a tumor (benign or malignant) of the base of skull requiring either definitive or post-operative radiation to a minimum prescribed dose of 45 Gy.

Study subjects deemed capable of undergoing standard CT simulation and radiotherapy treatment planning and delivery including the capacity to comply with standard immobilization devices to the head and neck for daily irradiation.

Study subjects without any evidence of distant metastasis.

Study subjects with an estimated life expectancy of at least 1 year.

Study subjects who are able to receive a standard MRI study and deemed capable of complying with the immobilization needs.

Female study subjects of reproductive potential with a negative pregnancy test prior to each scheduled MRI study.

Adequate bone marrow function and renal function: WBC greater than or equal to 4000/mm^3, platelets greater than or equal to 100,000 mm^3 and Creatine clearance of greater than 45.

Inclusion Criteria for Cohort 2 (Patients with Low Grade Gliomas or meningiomas)

Patients must be able to provide informed consent.

4.2.2 Study subjects with an ECOG performance status of 0-1 or KPS of 60-100.

4.2.3 Age greater than or equal to 18.

4.2.4 Histological confirmed diagnosis of low grade glioma (WHO grade II) or meningioma (WHO grade I) of the CNS.

4.2.5 Subjects deemed capable of undergoing standard CT simulation and radiotherapy treatment planning and delivery including the capacity to comply with standard immobilization devices to the brain for daily irradiation.

4.2.6 Patients with no evidence of distant metastases.

4.2.7 Adequate bone marrow function and renal function: WBC greater than or equal to 4000/mm^3, platelets greater than or equal to 100,000 mm^3 and Creatine clearance of greater than 45.

4.2.8 Women of child-bearing potential as long as she agrees to use a recognized method of birth control (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Hysterectomy or menopause must be clinically documented.

Exclusion Criteria for Both Cohorts

Study subjects with a Karnofsky performance status less than 60 or ECOG 2-4 whose life expectancy is less than 1 year.

Study subjects with anxiety that precludes the safe administration of a MRI for the imaging time required.

Study subjects with major documented psychiatric diagnosis prior to neuro-oncologic diagnosis.

For neuropsychological studies, study subjects with neurological or behavioral issues that would preclude compliance with study procedures.

Study subjects with an inability to undergo MR Imaging for any reason.

4.3.6 Study subjects with a history of renal transplant or known renal disorder with a calculated GFR > 45mL/1min [gadolinium restriction] *(SEE Attachment B FOR CALCULATION INFORMATION)*

4.3.7 Study subjects must be fluent in English.

4.3.8 Pregnant women, women planning to become pregnant and women who are nursing.

4.3.9 Prior or simultaneous malignancies within the past two years (other than cutaneous squamous or basal cell carcinoma, melanoma in situ or well differentiated thyroid carcinoma)

4.3.10 Additional Exclusion Criteria for Cohort 2 (Patients with Low Grade Gliomas or meningiomas)

4.3.10.1 Patients with the following histologies are excluded: gliomatosis cerebri, WHO III or IV gliomas

Subject Recruitment and Screening

Subjects will be recruited from the Oncology practices from either the Department of Defense oncology practices or by Penn Medical Center. Potential study subjects will also be identified from both weekly head and neck/brain tumor conferences and skull base tumor conferences held at the Hospital of the University of Pennsylvania. No advertisement will be used for study recruitment. Subjects will undergo an informed consent process in accordance

with GCP. Informed consent will be obtained prior to the performance of any screening procedures. Subjects must meet all of the inclusion and none of the exclusion criteria as determined by pre-treatment battery measures. The treating radiation oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist will contact a qualified member of the research team in the Radiation Oncology department at the University of Pennsylvania and initiate introduction to that team member. This research team member will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The volunteer nature of research will be stated and advice offered to the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which any screening procedures will be performed. A series of questions will be asked to verify patient eligibility based upon the inclusion/exclusion criteria. After the eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all radiation treatment in the Radiation Oncology clinic of the University of Pennsylvania.**

Normal participants will be recruited from the family, friends, and community members of the patients in the Department of Radiation Oncology. This technique was used previously in our studies of longitudinal effects of (photon) radiotherapy, and of normal aging. It has also been found to be successful in achieving target recruitment goals, in achieving the objective of matching patients with normals by age and education, and in recruiting normal who are generally from the same socioeconomic and cultural group as patients.

Normal subjects who volunteer to participate will be given brief interviews to identify their age and education, histories of developmental delays, learning difficulties, head injury, current psychiatric treatment, or a medical disorder that could affect learning, and medications currently being taken. Inclusion criteria are based on the age, education, and gender of the combined patient cohorts, so that the normal subject mean on these variables will not be significantly different from the patient cohort overall mean. Normal subjects must use English as their primary language or be bilingual in English. Exclusion criteria are histories of developmental delays, dyslexia or other learning disability, head injury, neurological disorder, other medical disorder than affects learning, current psychiatric treatment, complaints of major memory difficulty, and current use of medications for one of these disorders.

Early Withdrawal of Subjects

When and How to Withdraw Subjects

Study subjects may be withdrawn from the study prior to the expected completion for the following reasons:

Study subjects showing disease progression.

Study subjects expressing a wish to discontinue study participation.

Study subjects unable to comply with the time and immobilization needs of the MRI studies.

Data Collection and Follow-up for Withdrawn Subjects

The study data for withdrawn subjects will be analyzed. Withdrawn subjects will continue to be followed according to the routine follow-up schedule for their oncologic care. As survival is not a study endpoint, and the study does not involve a therapeutic intervention, survival data for withdrawn subjects will not be formally collected as a study requirement.

Study Procedures

See Section 3 for description of specific neurocognitive testing and MR imaging and procedure table.

Visit 1 (before the start of radiation therapy)

Study subjects will have a baseline research neurocognitive evaluation, anticipated to require approximately 4-5 hours. MRI study acquiring anatomic, perfusion, spectroscopy, and diffusion is anticipated to require approximately 60 minutes.

Visit 2 at approximately 1.5 months after completion of radiation for both cohorts, same procedures as above.

Visit 3 at approximately 6 months after completion of radiation for both cohorts, will undergo the same procedures as above.

Visit 4 at approximately 12 months after completion of radiation therapy for both cohorts, will undergo the same procedures as above.

Visit 5 at approximately 24 months after completion of radiation for both cohorts, will undergo the same procedures as above.

Primary and secondary endpoints will be acquired at all time points

6.0 STATISTICAL PLAN

6.1 STUDY DESIGN

This is a longitudinal, observational study of brain imaging and neurocognitive testing in patients with either head and neck/skull base tumors (benign or malignant) or low grade glioma or meningioma who are receiving radiation therapy. Patients will be stratified by site of disease. **The over-arching hypothesis is that dose reduction to normal brain tissue provided by proton therapy will reduce both brain injury and neurological deficits.**

We will enroll 20 patients with head and neck/skull base tumors (benign or malignant) who are being treated with protons over 3 years. Prior to the activation of the proton clinical trial, approximately 10 patients being treated with photons will be enrolled and will serve as contemporary controls.

We will enroll 40 patients with low grade glioma or meningioma who are being treated with protons over 3 years. The proton clinical trial is already activated and all low grade glioma or meningioma patients treated by the Department will be treated with protons. Two historical cohorts of 40 PENN glioma patients treated with photons and 30 untreated PENN glioma patients, who had neurocognitive testing on the identical schedule, will serve as the control groups.

Neurocognitive test data will be collected from the normal normal group (70 patients) only for the four tests of cerebellar-specific function: Audio-Visual Attention Shifting Test, Serial Response Task, Balls in a Bottle Test, and Timing Functions Test. The values from the normal group will add to the longitudinal analyses by permitting us to describe a level of clinical impairment, if any, in the patients at the longitudinal time points.

6.2 *OBJECTIVES (FOR BOTH COHORTS)*

1. Assess cognitive changes over three years, within and between patient groups, with analyses within the first year, and at years two and three.

2. Examine other clinical variables that may exacerbate (or protect) patients from functional damage from irradiation.

3. Investigate the association of specific cognitive variables with associated imaging regions of interest.

6.3 *ENDPOINTS*

6.3.1

Structural imaging variables, see Sections 3.4.1.-3.5.
Neurocognitive variables, see Section 3.5.1.

6.3.3 Assessment Times

Neurocognitive tests will be performed at approximately: baseline (prior to radiotherapy),1.5 and 6 months after completion of radiation and then annually approximately at 12 and 24 months for both cohorts. MRI testing will be performed for both cohorts at approximately : baseline, 1.5, 6, 12 and 24 months after completion of radiation treatment.

6.3.4 Baseline and Treatment Variables and Time varying Covariates

Baseline and treatment variables, such as age, radiation dose, treatment volume, will be included. Medications will be coded as four dichotomous time varying covariates: anti-hypertensives, anti-seizure, steroids and anti-depressants.

6.4 *STATISTICAL ANALYSES (FOR BOTH COHORTS*)

General Methods: Graphical methods, including histograms, scatterplots, boxplots, and mean plots of time trends will be generated, to understand data quality and variability. Mean, median, range, and standard deviation will be computed for all continuous variables. Frequencies and percentages will be computed for categorical and ordinal variables. Prior to hypothesis testing and modeling, we will consider transformation to Z-scores for scales for which population normative values are well established. For variables that exhibit markedly skewed distributions, appropriate transformations, such as natural logarithm, will be applied. Pearson's correlation will be employed to assess correlation between imaging and neurocognitive measures taken at the same time points.

Hypothesis Testing: Neurocognitive function, memory in particular, significantly declined from baseline to 1.5 months post-completion of radiotherapy in low grade glioma patients treated with photons. A gradual rebound beginning 6 months post-completion of radiotherapy and continuing through at least one year of follow-up was observed. We hypothesize that in proton-treated patients, the decline at 1.5 months will be reduced, and that larger positive slopes of change in cognitive function will emerge by the last study time point, two years post treatment (one or two years post treatment in some patients recruited later in the study).

For Aim 1, a primary objective is to evaluate within-patient changes from baseline to one year. For the proton-treated group, within-patient change will be tested by paired t test. Within-patient trends over time will be analyzed with linear mixed effects models. To model the early decline and then rebound, piecewise linear or quadratic functions will be evaluated. Linear mixed effects models are available in several statistical software packages, such as the *xtmixed* procedure in STATA. Missing data are common in longitudinal studies. The *xtmixed* procedure allows unbalanced data, enabling us to analyze all data collected. In addition, we will assess the impact of the missing data on model estimates by conducting sensitivity analyses that make different assumptions about the missing data mechanism. For example, we will use multiple imputation to impute missing values assuming a missing at random (MAR) mechanism, that allow missing data to depend on measured variables such as age and sex. Another primary objective is to evaluate between-group differences in these changes from baseline to one year, which will be assessed by independent groups t test or by repeated measures ANOVA. Trends over time will be compared among the untreated, photon and proton radiation groups using linear mixed effects models, in which a time by group interaction term is included. The analysis strategy described above will also be applied to longitudinal brain imaging data.

For Aim 2, to examine clinical variables that may exacerbate (or protect) patients from functional damage, linear mixed effects models will be extended to include baseline fixed effects and time varying covariates.

For Aim 3, to investigate the correlation between longitudinal neurocognitive measurements and longitudinal brain imaging measurements which are measured at the same time points, linear mixed effects models will include repeated brain imaging outcomes as random effects.

6.4 SAMPLE SIZE/POWER

6.4.1 *Skull Base*

With 20 proton patients enrolled, a within-patient change of 0.85 SD_{diff} units between baseline and 1.5 months post-completion of radiation, can be detected with 81% power by paired t-test at a reduced 2-sided 1% significance level. With 20 proton patients and 10 photon patients, a difference in mean change from baseline to 1.5 months of 1.5 SD units between groups can be detected with at least 85% power by 2 independent group t-test at a 2-sided 1% significance level.

There are no preliminary longitudinal neurocognitive data in skull base patients treated with photons or protons. Comparison of slopes will also be tested with a linear mixed effects model. If we find that the trend is linear throughout the entire time interval from baseline, then the model will include 5 repeated measures. Otherwise, assuming the linear mixed model is focused on the rebound in the time interval from 1.5 to 24 months post-radiation, and the following inputs: 15 patients per group, 4 repeated measures, 0.01 type I error, 80% power, correlation = 0.5, SD_X^2 =100.5 and SD_Y^2 = 12.5, an effect size of 0.18 words/month can be detected. Because of the smaller sample size in this group and our lack of preliminary data, these analyses will be more exploratory and focus on estimation of trajectories over time rather than hypothesis testing.

6.4.2 *Low Grade Glioma or Meningioma*

With 40 proton patients enrolled, a within-patient change of 0.6 SD_{diff} units between baseline and 1.5 months post-completion of radiation, can be detected with 85% power by paired t-test at a reduced 2-sided 1% significance level to control for multiple comparisons arising from many neurocognitive tests. With 40 proton patients and 40 historical photon patients, a difference in mean change from baseline to 1.5 months of 0.8 SD units between groups can be detected with 82% power by 2 independent group t-test at a 2-sided 1% significance level. Comparison of 40 proton patients to 30 untreated controls would have 80% power to detect a 0.85 SD unit difference.

We have preliminary longitudinal data on the 'Delayed Recall Word List' memory test from 40 photon radiated glioma patients and 30 untreated glioma patients (Armstrong et. al. manuscript in progress). Patients were given this memory test at baseline and at 1.5, 6 and 12 months after completion of radiation. The patients were asked to memorize a list of 15 words. After a time delay, they were then asked to recall the word list. The grand mean $\pm$ SD of the number of words recalled, for all 70 patients pooled over all time points was 10.38 $\pm$ 3.54 words (SD^2 = 12.53). Data for each group at each time point were:

		Months from the completion of radiation			
Observed values		baseline	1.5	6	12
Mean # words	Radiation	10.20	8.45	9.53	10.69
Untreated		11.45	11.33	11.72	11.47

If proton therapy reduces neurological deficits as expected, then the proton group may exhibit little change in memory function, similar to the untreated group.

In a linear mixed effects model, the comparison of slopes would focus on the gradual rebound in the time interval from 1.5 to 24 months from completion of radiation. Using the formula on page 30 of Diggle et. al. *Analysis of Longitudinal Data*, an R program was written to calculate effect size. The table below displays detectable effect sizes (i.e., difference in slopes between two groups) assuming the following inputs: 40 patients per group, 4 repeated measures, 0.01 type I error, 80% power, correlation = 0.5, SD_X^2 = 100.5 (from time points 1.5, 6, 12 and 24 months from end of radiation) for a range of values of SD_Y^2.

Variance of outcome, SD_Y^2	Detectable Effect size (words/month)

8	0.09
10	0.10
12	0.11

Assuming variance of 12, slope = 0 for proton patients, a model of slopes over the 1.5 to 24 months from completion of radiation interval and slope = 0.11 words/month for photon patients, the expected between-group differences are shown in the table below.

		Months from the completion of radiation			
Expected values		1.5	6	12	24
Mean # words	Photon	8.5	8.8	9.7	11.0
	Proton	11.5	11.5	11.5	11.5
Between-group Difference		3.0	2.7	1.8	0.5

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.
All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

7.2 Reporting of Serious Adverse Events and Unanticipated Problems

7.2.1 IRB Notification by Investigator
All events meeting the Penn IRB SOP for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:
(1) Unforeseen; and (2) indicate that participants are at increased risk of harm. The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**. The one exception for prompt reporting within 10 days applies to death of a research participant as noted below.

Adverse Event (regardless of whether the event is serious or non-serious, onsite or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is both unexpected and related to research procedures.

Note: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts); An event is "related to the research procedures" if the event is deemed probably or definitely related.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

7.2.2 Data and Safety Monitoring Committee (DSMC) Notification by Investigator
All Serious Adverse Events (SAEs), regardless of grade, expectedness or attribution must be reported to the DSMC within 30 days. Deaths that are possibly, probably or definitely related to the protocol treatment/experience must be reported within 24 hours. SAEs should be reported to the DSMC for six months from the date the last subject was treated.

7.2.3 USAMRMC, Office of Research Protections, Human Research Protection Office Notification (ORP, HRPO) by Investigator

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

7.3 Medical Monitoring
It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. "The medical monitor will provide an unbiased written report of the event to include comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship of the event to participation in the study. The medical monitor must also indicate whether she/he concurs with the details of the report provided by the principal investigator".

The Medical Monitor will be Amy Pruitt, MD (a physician who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial). Because of Dr. Pruitt's background and experience she is an appropriate Medical Monitor (MM) for this study. In the role, she will review all AEs including grading, toxicity assignments, dose modifications, and all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and similar investigational agents. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The investigator will meet with the Medical Monitor every year.

Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of Medical Monitor activity will be maintained in the study specific Regulatory Binder. Copies of a Medical Monitor report requiring action on the part of the PI to protect subject safety or study integrity must be submitted to the DSMC within 10 business days.

7.3.1 Data and Safety Monitoring Committee

The University of Pennsylvania Cancer Center (UPCC) through the Data and Safety Monitoring Committee (DSMC) will be reviewing this clinical trial. It is anticipated that with approval, the committee's role will be to ensure that the rights and well-being of all subjects are protected and that patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data and Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

A Medical Monitor, Amy Pruitt, M.D., who is not directly involved in this trial and is not collaborating with the investigator in any other trials, has been selected for this trial. The Medical Monitor will review adverse events, safety data, and activity data observed in the ongoing clinical trial. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial. The summary reports of all discussions of adverse events will be submitted to the Data and Safety Monitoring Committee (DSMC) on an annual basis or more frequently if appropriate.

The Principal Investigator or his/her designee of the trial will present to the Medical Monitor all adverse events observed inpatients, any activity data obtained, and whether those data invoked any stopping criteria in the clinical protocol. Adverse event reporting will follow the NCI guidelines. Results of the data from toxicology or other animal studies that are relevant will be discussed. Other information related to the safety and efficacy of the clinical study will be discussed. This includes information of similar investigational materials used in different studies.

7.4 *Protocol Deviations/Exceptions*

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

All deviations from the study protocol will be handled as follows:

7.4.1 *Eligibility*

Deviations from established eligibility criteria will not be allowed. If the investigator believes that a subject would truly benefit from the protocol therapy and there are no other viable options, then the protocol should be amended to reflect the change in restrictions. There may be situations where the deviation from eligibility may not warrant a study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, subject taking a concomitant medication within recent timeframe etc.). These deviations must still be reviewed and approved in advance of enrolling the subject.

The IRB must be notified of the planned deviation and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. The DSMC does not approve deviations but rather provides and unbiased assessment of the appropriateness of the request. Both committees must be given sufficient time to review the request, gather additional information as necessary and make a decision**.** The Medical Monitor will be consulted first for all such deviations. Documentation of the Medical Monitor's assessment and opinion will be included with the initial report to both committees.

7.4.2 *Other Reportable-* Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.

7.4.3 *Non-Reportable-* During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. subject not showing up for a study visit, lab errors, subject confusion etc.). These type of

deviations are not reportable (unless they occur at a level that impacts any of the reportable categories) but must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that were taken. Documentation can be in the clinic/progress notes or note/memo to file. Notes/memos should be signed and dated.

7.4.4 *Reporting Deviations/Exceptions*

Reports to the IRB and DSMC will be done via the electronic Clinical Trials Management System, Velos. Reportable deviations must also be sent to the study Medical Monitor (if applicable). A report will also be filed to USAMRMC, Office of Research Protections, Human Research Protection Office.

8.0 Data Handling and Record Keeping

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

Confidential research charts will be kept in locked cabinets at each participating institution. Subjects will be assigned a study number at the time of study enrollment. This study number and not the subject's name will be used on all case report forms.

8.1 *HIPAA Compliance:*

Patients will be asked to read and sign a combined informed consent form and HIPAA authorization form acknowledging the uses and disclosures of protected health information (PHI) in this study as required by The Health Insurance Portability and Accountability Act (HIPAA). PHI will not be shared with any outside institution except as required by law. Any reporting of the results of this study will be done only with de-identified patient data. Confidentiality will be protected as outlined below.

- Each subject will sign a study combined informed consent and HIPAA authorization form prior to study enrollment.
- Each subject will be assigned a study number. All research-related material (to include specimens for research) will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained in a locked cabinet and computer by the principal investigator and study coordinator.
- All research subject records will be kept in a study chart or in the electronic CTMS, Velos.

8.2 Data Entry

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study. Case report forms will be used to standardize data-keeping.

8.3 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subject(s) in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.3.1 Unintentional Disclosure

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it etc.). A report will also be filed to USAMRMC, Office of Research Protections, Human Research Protection Office.

8.4 Records Retention

8.4.1 Federally Funded Research or Non-IND/IDE Research

The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

8.4.2 HIPAA Retention Period (45 CFR164.530(j):

Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 6 years after the research is fully terminated.

9 0 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

The University of Pennsylvania Cancer Center (UPCC) has a formal plan for Data Safety and Monitoring of Clinical Trials. The clinical trial, "Detection of Vascular and Neuronal Changes and their Correlation to Neurocognitive Changes Following Proton and Photon Radiotherapy in Patients Receiving Skull Base and Brain Radiation" is a trial that is subject to oversight of the UPCC through the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC). The CTSRMC role is to ensure that the rights and well-being of all subjects are protected and that patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

A DSMC audit of this trial will be performed twice a year for as long as the trial remains open for accrual. However, this schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling

studies will be audited more frequently as necessary. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected subjects or 10% of the total accrual (up to 10 subjects), whichever is higher, are audited. A formal report is written to the PI within about 5 business days of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, representatives from the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status. The PI is given five business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the Administrative Director do not find the response satisfactory, the IRB and OHR will be alerted of the actions taken by the ACC. The DSMC Administrative Director will update the IRB and OHR of the corrective actions being taken and progress being made.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study is being funded by a grant from the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

13 References

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Attachment A

Protocol Addendum

Detection of Vascular and Neuronal Changes and their Correlation to Neurocognitive Changes Following Proton and Photon Radiotherapy in Patients Receiving Skull Base and Brain Radiation

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(5) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(6) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

Attachment B

Glomerular Filtration Rate (GFR) Calculation

Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age.

In adults the best equation for estimating glomerular filtration rate (GFR) from serum creatinine is the Modification of Diet in Renal Disease (MDRD) Study equation. The original MDRD Study equation GFR Calculator is for use with routine creatinine methods. The IDMS-traceable MDRD Study equation GFR Calculator is for use with those methods that have been recalibrated to be traceable to IDMS.

http://nkdep.nih.gov/professionals/gfr_calculators/orig_si.htm

FEDERAL FINANCIAL REPORT

(Follow form instructions)

1. Federal Agency and Organizational Element to Which Report is Submitted	2. Federal Grant or Other Identifying Number Assigned by Federal Agency (To report multiple grants, use FFR Attachment)	Page	of
Department of The Army	W81XWH-09-2-0174	1	1 pages

3. Recipient Organization (Name and complete address including Zip code)

University of Pennsylvania
3451 Walnut Street, Franklin Bldg. P-221
Philadelphia, PA 19104-6205

4a. DUNS Number	4b. EIN	5. Recipient Account Number or Identifying Number (To report multiple grants, use FFR Attachment)	6. Report Type	7. Basis of Accounting
04-225-0712	23-1352685	553642(#10)	X Quarterly □ Semi-Annual □ Annual □ Final	X Cash □ Accrual

8. Project/Grant Period From: (Month, Day, Year)	To: (Month, Day, Year)	9. Reporting Period End Date (Month, Day, Year)
9/24/2009	9/30/2015	9/30/2013

10. Transactions	Cumulative
(Use lines a-c for single or multiple grant reporting)	
Federal Cash (To report multiple grants, also use FFR Attachment):	
a. Cash Receipts	$6,787,000.00
b. Cash Disbursements	$4,477,337.19
c. Cash on Hand (line a minus b)	$2,309,662.81
(Use lines d-o for single grant reporting)	
Federal Expenditures and Unobligated Balance:	
d. Total Federal funds authorized	$6,787,000.00
e. Federal share of expenditures	$4,477,337.19
f. Federal share of unliquidated obligations	$0.00
g. Total Federal share (sum of lines e and f)	$4,477,337.19
h. Unobligated balance of Federal funds (line d minus g)	$2,309,662.81
Recipient Share:	
i. Total recipient share required	$0.00
j. Recipient share of expenditures	$0.00
k. Remaining recipient share to be provided (line i minus j)	$0.00
Program Income:	
l. Total Federal program income earned	
m. Program income expended in accordance with the deduction alternative	
n. Program income expended in accordance with the addition alternative	
o. Unexpended program income (line l minus line m or line n)	

	a. Type	b. Rate	c. Period From	Period To	d. Base	e. Amount Charged	f. Federal Share
11. Indirect Expense	Predetermined	59.90%	9/24/2009	6/30/2010	$ 185,296.80	$ 110,992.78	$ 110,992.78
		60.00%	7/1/2010	9/30/2013	1,063,824.62	$ 638,294.77	$ 638,294.71
			g. Totals:		1,249,121.42	749,287.56	$ 749,287.50

12. *Remarks: Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation:*

13. Certification: By signing this report, I certify that it is true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent information may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

a. Typed or Printed Name and Title of Authorized Certifying Official	c. Telephone (Area code, number and extension)
Elvina Woodard Manager, Research Services	215-898-3148
	d. Email address elvina@upenn.edu
b. Signature of Authorized Certifying Official Elvina Woodard	e. Date Report Submitted (Month, Day, Year) 10/8/13
	14. Agency use only:

Standard Form 425
OMB Approval Number: 0348-0061
Expiration Date: 10/31/2011

QUARTERLY REPORT FORMAT

1. Award No. W81XWH-09-2-0174 2. Report Date 10/15/2013

3. Reporting period from July 1, 2013 to September 30, 2013

4. PI Zelig Tochner 5. Telephone No. 215-662-6934

6. Institution University of Pennsylvania, Department of Radiology Oncology

7. Project Title "Proton Therapy dose Characterization and Verification"

8. Current staff, with percent effort of each on project.

Tochner, Zelig	10%	Zhu, Timothy	5%
Hill-Kayser, Christine	10%	Smith, Deborah	5%
Finlay, Jarod	10%	Gabriel, Peter	20%
Alonso-Basanta, Michelle	6%		
Mangaali, Margaret	95%	Panetta, Joseph	100%
Ashley Feriozzi	55%	Tang, Shikui	50%

9. Award expenditures to date (as applicable):

	This Qtr/Cumulative		This Qtr/Cumulative
Personnel	63,352.07 / 725,127.33	Travel	0.00 / 5,274.12
Fringe Benefits	20,145.96 / 225,386.26	Equipment	0.00 / 2,105,359.65
Supplies	0.00 / 6,908.73	Other	59,544.02 / 659,993.60

	This Qtr/Cumulative
Subtotal	143,042.05 / 3,728,049.69
Indirect Costs	55,288.65 / 749,287.50
Fee	/
Total	198,330.70 / 4,477,337.19

10. Comments on administrative and logistical matters.

11. Use additional page(s), as necessary, to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this assistance agreement.

12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

Elvina Woodard 10/8/13

Elvina Woodard
Assistant Director